

# **Pediatric Hematology**

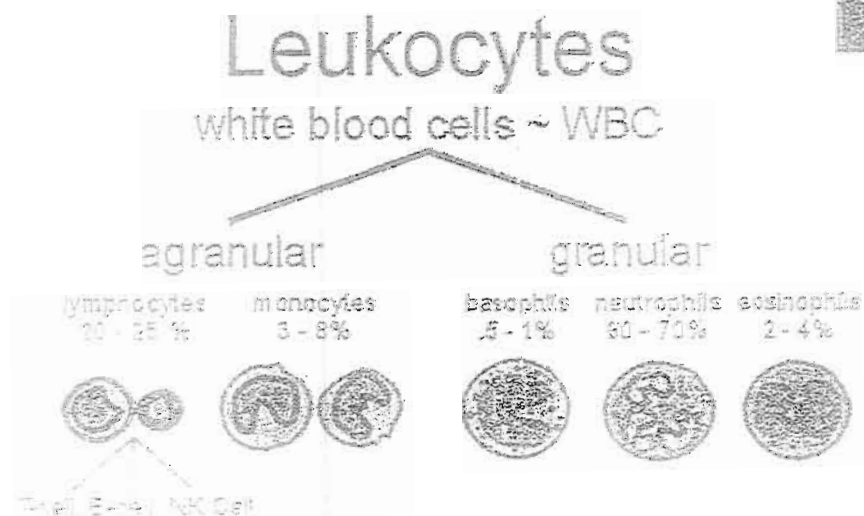
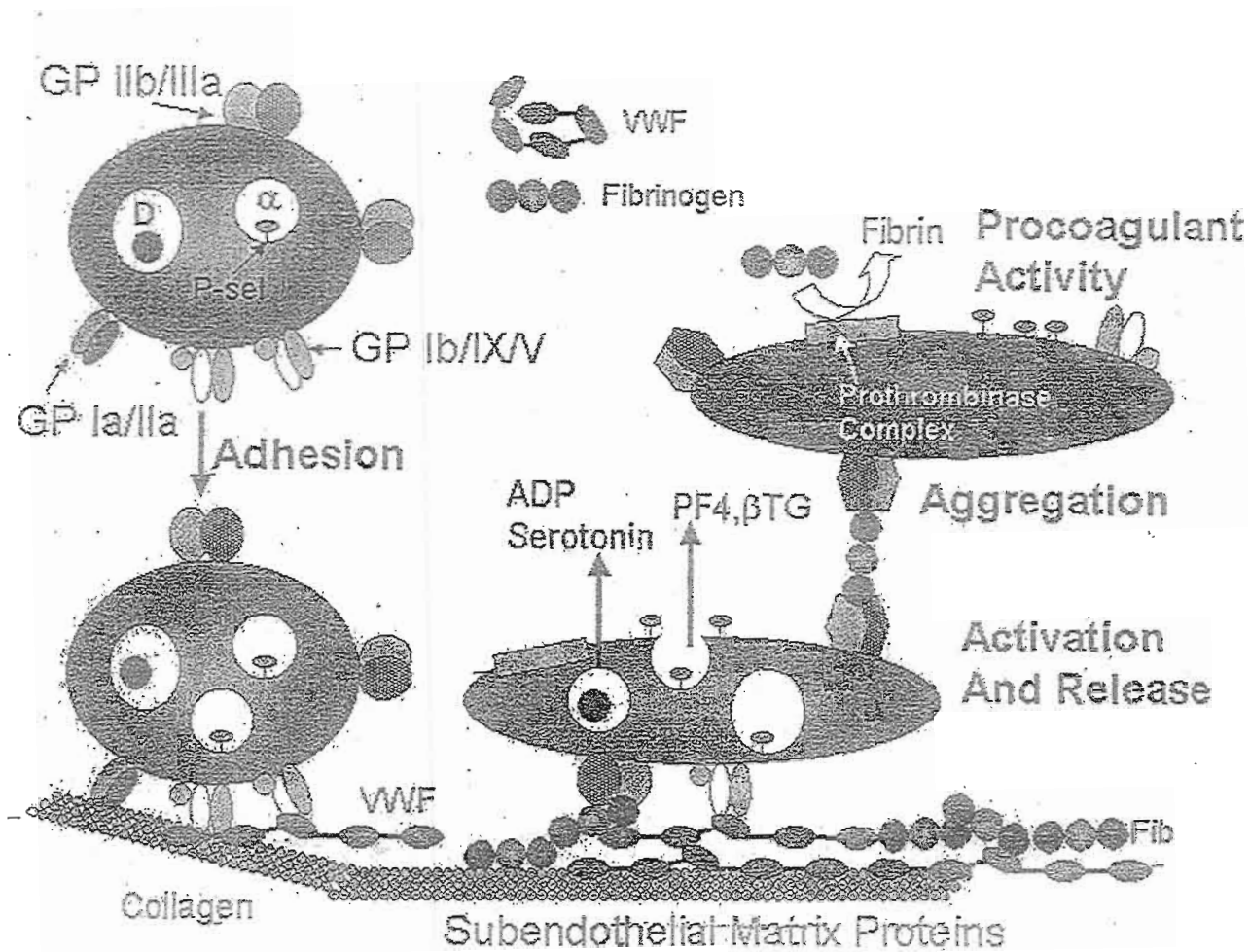
**By**

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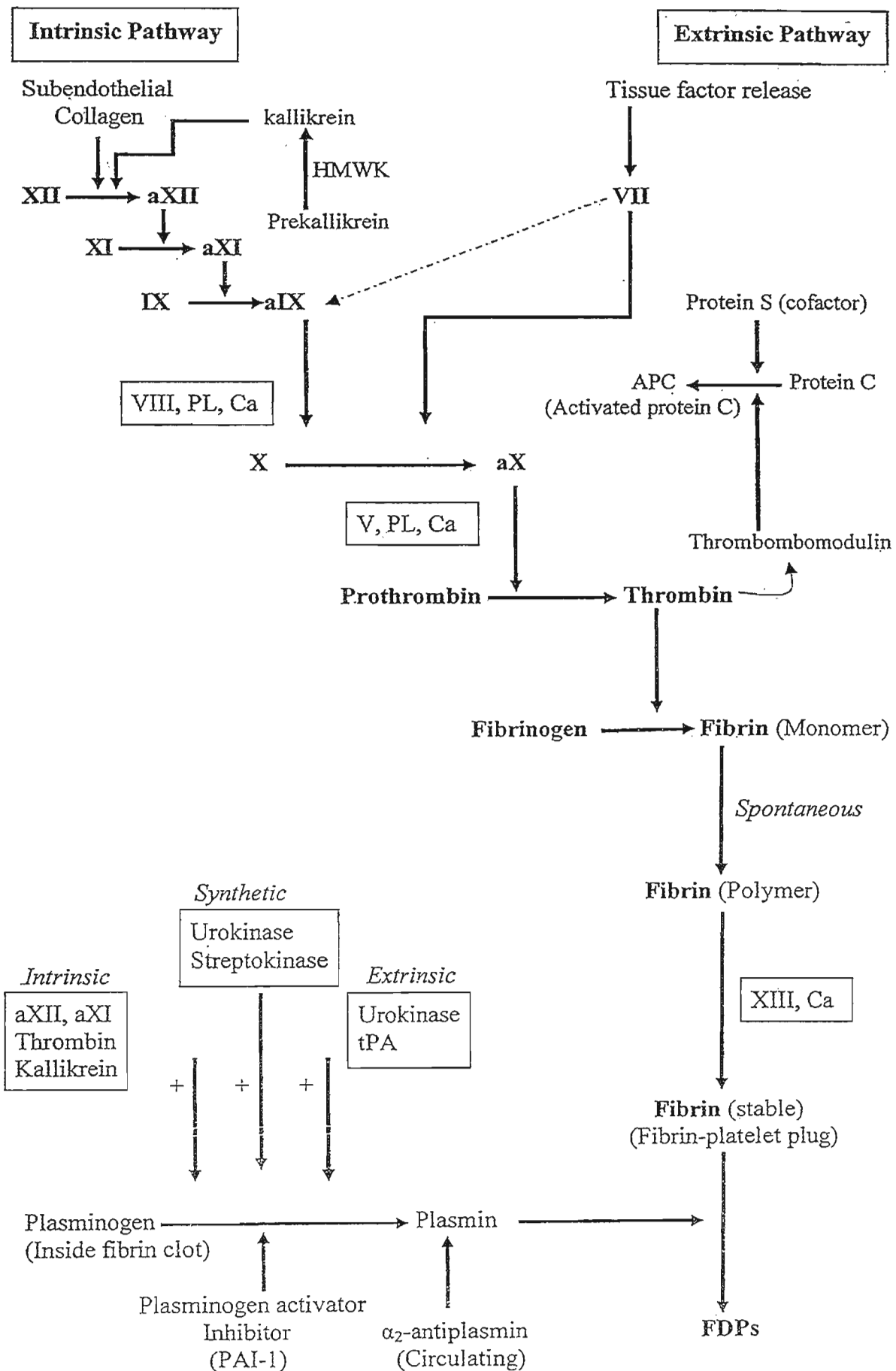
**2012**

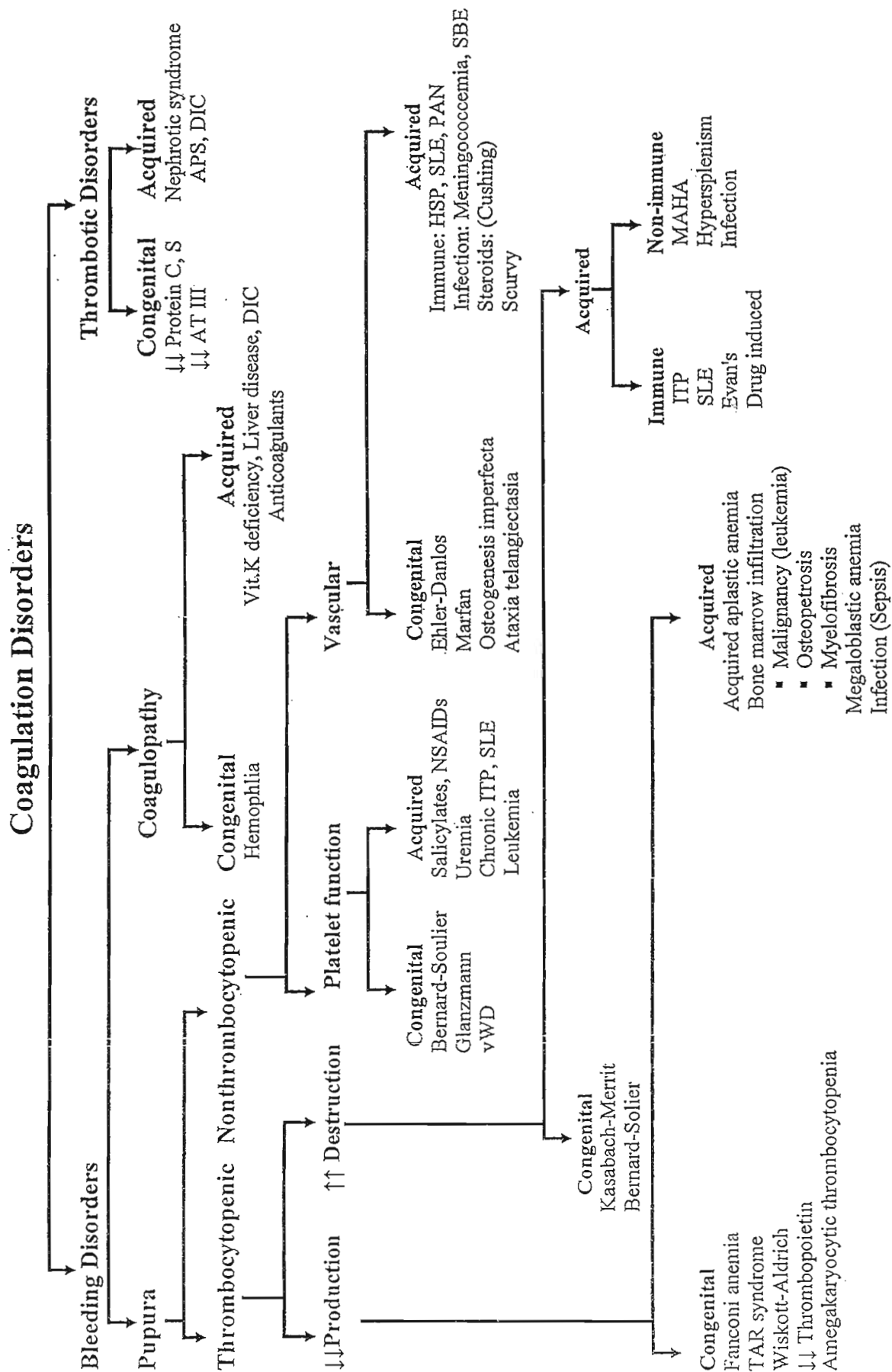




# Hemostasis

Function	Vasculature	Platelet	Coagulation	Plasma Factors (Fibrinolysis, Plasmin)	Natural anticoagulants
<b>1. VC</b> <ul style="list-style-type: none"><li>▪ Reflex</li><li>▪ Serotonin (Platelet)</li></ul> <b>2. Exposure of subendothelial matrix</b> <ul style="list-style-type: none"><li>▪ ↑↑ vWF (Plt adhesion)</li><li>▪ ↑↑ XII</li></ul> <b>3. Release of (↑↑ Intrinsic pathway)</b> Tissue thromboplastin → ↑↑ VII (↑↑ Extrinsic pathway)	<b>1. Adhesion to subendothelial matrix (vWF mediated)</b> <b>2. Aggregation</b> By ADP " Thromboxane A <sub>2</sub> <b>3. Release</b> " Serotonin (VC) & TXA <sub>2</sub> " ADP (aggregation) " Phospholipids (PL) " Thromboxthenin → (clot retraction) <b>4. Platelet plug formation</b> <b>5. Stabilization of fibrin platelet plug by XIII</b>	<b>1. Phase I (formation of prothrombinase)</b> <ul style="list-style-type: none"><li>▪ Intrinsic pathway XII, XI, IX, VIII, X, V</li><li>▪ Extrinsic pathway Tissue thromboplastin, VII, X, V</li></ul> <b>2. Phase II</b> Prothrombin → Thrombin <b>3. Phase III</b> Fibrinogen → Fibrin monomer → Polymer <b>4. Phase IV (Stabilization of fibrin polymer by XIII)</b>	<b>Essential mechanism:</b> <ul style="list-style-type: none"><li>▪ # Extension of the clot</li><li>▪ BV patency</li></ul> <b>1. Activators</b> <ul style="list-style-type: none"><li>▪ <u>Intrinsic</u>: aXII, aXI, Kallikrein, Thrombin</li><li>▪ <u>Extrinsic</u>: Urokinase, tPA (tissue plasminogen activator)</li><li>▪ <u>Synthetic</u>: Urokinase, Streptokinase</li></ul> <b>2. Inhibitors</b> <ul style="list-style-type: none"><li>▪ Plasminogen activator inhibitor (PAI-1)</li><li>▪ α<sub>2</sub> antiplasmin</li></ul>	<b>1. Euglobulin clot lysis time (ELT):</b> (N = 2-4 hrs) Short ELT: <ul style="list-style-type: none"><li>▪ ↑↑ Plasminogen activators</li><li>▪ ↓↓ Fibrinogen</li></ul> Prolonged ELT: <ul style="list-style-type: none"><li>▪ ↓↓ Plasminogen</li><li>▪ ↓↓ Plasminogen activators</li><li>▪ ↑↑ Fibrinogen</li></ul> <b>2. Plasminogen</b> <b>3. Plasminogen activators &amp; inhibitors</b> <b>4. Fibrin degradation products (FDPs)</b>	<b>1. Protein C</b> Activated by thrombin-thrombomodulin complex → APC → Inactivates aV, aVIII ( <i>Thrombomodulin is present on the intact endothelial surface</i> ) <b>2. Protein S</b> Cofactor for protein C <b>3. Antithrombin III</b> # Thrombin, X, IX, XI, XII <b>4. Tissue factor pathway Inhibitor (TFPI)</b> ↓↓ activation of X by VII
<b>1. Hess test (Tourniquet test)</b> (N = <5 petechiae in 2.5 cm <sup>2</sup> ) <ul style="list-style-type: none"><li>▪ Blood vessel</li><li>▪ Platelet (No &amp; function)</li></ul> <b>2. Bleeding time (4-8 min)</b> <ul style="list-style-type: none"><li>▪ Blood vessel</li><li>▪ Platelet (No &amp; function)</li></ul> <b>3. Platelet No.</b> Platelets are essential for BV integrity	<b>1. Platelet count</b> (150,000-400,000/mm <sup>3</sup> ) Patients with count >50,000 rarely have significant bleeding <b>2. Bleeding time</b> <b>3. Platelet function</b> <ul style="list-style-type: none"><li>▪ Adhesion</li><li>▪ Aggregation (ristocetin, collagen, ADP)</li><li>▪ Clot retraction</li><li>▪ vWF (Ag &amp; activity)</li></ul>	<b>1. Phase IV</b> 5M urea test (soluble clot) <b>2. Phase III</b> Fibrinogen assay Thrombin & Reptilase time (N = 11-15 sec) <b>3. Phase I, II</b> Specific factors PT (10-13 sec) = VII, X, V, II PTT (25-40 sec) = XII, XI, IX, VIII, X, V, II Corrected by plasma = VIII Corrected by serum = IX Corrected by Both = XI Not corrected = XII <b>4. Coagulation time (8-12)</b>	<b>1. Measurement of</b> <ul style="list-style-type: none"><li>▪ Protein C</li><li>▪ Protein S</li><li>▪ Antithrombin III</li></ul>		





# Bleeding Disorders

## Classification

a. Purpura

b. Coagulopathy

## General Features

	Purpura	Coagulation disorders
<b>Defect</b>	Platelet or vessel wall	Coagulation factors
<b>Skin lesions</b>	Petechiae 1-2 mm Ecchymosis 1-2 cm	Ecchymosis
<b>Site of bleeding</b>	Mucous membranes (mouth, gums, epistaxis, conjunctiva) Internal Hge (ICH) less common	Deep bleeding; joints (hemoarthrosis), muscle (hematoma)
<b>Relation to trauma</b>	Immediate Usually spontaneous	Usually delayed (oozing) Usually traumatic

# Coagulation Disorders

## Classification

a. **Inherited:** Hemophilia (A,B,C), vWD & other coagulation factor deficiencies

b. **Acquired:** vitamin K deficiency, advanced liver disease, DIC, anticoagulants & acquired inhibitors of coagulation (APS, following Rx with F VIII or IX )

## Hemophilia A (Classic hemophilia)

### Definition

It is the commonest cause of hemophilia (85%). **Incidence** = 1: 5000 ♂

### Genetics& Etiology

- X-linked recessive (Its locus is close to that of G-6-PD & color blindness)
- Some female carriers of hemophilia may have mild bleeding (lyon hypothesis)
- 20% of cases are new mutations
- The hemostatic level of factor VIII is > 30-40 U/dL
- ↓↓ Factor VIII (intrinsic pathway). According to plasma level of factor VIII:

Factor VIII	Severity	Bleeding tendency
< 1 %	Severe	Spontaneous- Joint/muscle bleeding
1-5 %	Moderate	Bleeding after minor trauma
> 5-30	Mild	Bleeding after surgery

### Clinical picture

- Bleeding tendency may be evident in the neonatal period
- Post circumcision bleeding
- Easy bruising
- Unusual hematomas (muscle hematoma → fibrosis → contracture → deformity)
- Hemarthrosis is common (Pain, tenderness, swelling, flexion, tense overlying skin )
- Hematuria, epistaxis, bleeding gums, post-tooth extraction bleeding, ICH

### Investigations

- Coagulation time & PTT: ↑↑ (corrected by plasma)
- Factor VIII assay: ↓↓
- PT, TT, Bleeding time, platelet count: normal
- Prenatal diagnosis: Factor VIII assay in fetal blood (fetoscopy) & DNA study

## Treatment

### A) General measures

- Careful observation & psychological support
- Avoid trauma, salicylates & NSAIDs
- Avoid IM injection, deep veins for venipuncture (use superficial veins)
- HBV vaccine
- Hospitalization: head trauma, neck swelling & marked hemarthrosis

#### Avoid

- Trauma
- IM injection
- Deep veins
- NSAIDs

### B) Prophylactic therapy

- Factor VIII prophylactic therapy : in **severe** cases to prevent spontaneous joint bleeding  
It is given every 2-3 days (IV) to maintain factor VIII trough level 1-2 U/dL

### C) Management of bleeding (Half life of factor VIII= 12 hours)

- Recombinant factor VIII: supplied as powder (Recombinant DNA technology)  
Dose of factor VIII =  $0.5 \times \text{BW} \times [\% \text{ desired } \uparrow\uparrow \text{ in plasma F VIII}] \approx 20-40 \text{ U/Kg}$
- Lyophilized concentrate (freeze-dry): supplied as powder prepared from many donors  
( $\uparrow\uparrow$  risk of HIV & HBV transmission)
- Cryoprecipitate: fraction of 1 Unit frozen plasma (*It contains VIII, vWF, I, XIII*)
- Fresh frozen plasma: 10-15 ml/Kg/12 hours
- Desmopressin ( $0.3 \mu\text{g/Kg IV}$  or  $150-300 \mu\text{g intranasal}$ ): in **mild** cases (It  $\uparrow\uparrow$  endogenous factor VIII)
- Antifibrinolytic therapy in mucosal bleeding (epistaxis, mouth, dental...)

- ☒ Prednisone may be given in hemarthrosis & persistent hematuria
- ☒ Joint aspiration may be indicated in hip hemarthrosis to prevent avascular necrosis
- ☒ Antifibrinolytic therapy is contraindicated in hemarthrosis & hematuria
- ☒ Continuous infusion is needed in life threatening conditions & major surgeries

## Complications

- Chronic joint destruction and muscle atrophy & contracture
- Death (ICH, massive bleeding...)
- Complications of therapy:
  - ☒ Development of inhibitors (Ab):  $\downarrow\downarrow$  response to appropriate replacement therapy  
 Rx:
    - Continue** on regular dose (spontaneous Ab loss)
    - $\uparrow\uparrow$  **dose** to induce tolerance
    - Recombinant** FVII or prothrombin complex concentrate to bypass the defect
  - ☒ Transmission of blood born diseases (HIV, HBV, HCV, Parvovirus...)
  - ☒ Allergy, anaphylaxis, renal disease (immune complex disease)

## Hemophilia B & C

	Hemophilia B	Hemophilia C
Defect	F IX $\downarrow\downarrow$ (Christmas disease)	F XI $\downarrow\downarrow$
Half life	24 hrs	48 hrs
Incidence	10-15 %	2-3 %
Inheritance	X-linked recessive	Autosomal Recessive
C/P	As hemophilia A	Milder or No bleeding
Lab	F IX assay $\uparrow\uparrow$ PTT (corrected by serum)	F IX assay, $\uparrow\uparrow$ PTT (corrected by plasma & serum)
Treatment	F IX (Recombinant / lyophilized), FFP	FFP
	Desmopressin & Cryoprecipitate are <b>ineffective</b>	

## Other Coagulation Factor Deficiencies

	Defect	C/P	Lab	Treatment
<b>Factor XII Deficiency</b>	↓↓ F XII (Hageman F)	No bleeding ± may thrombosis (↓↓ plasminogen)	↑↑ PTT (Not corrected by plasma or serum), F XII	No Rx is needed
<b>Von Willebrand San Diego S</b>	↓↓ F XII + ↓↓ vWF	Mucocutaneous Bleeding	↑↑ PTT	As vWD
<b>Deficiency of contact factors</b>	↓↓ XII, HMWK ↓↓ Prekallikrein	No bleeding	↑↑ PTT	No Rx is needed
<b>Factor V Deficiency (Owren disease)</b>	↓↓ F V Parahemophilia (Labile factor)	Mucocutaneous bleeding, Hemarthrosis (rare)	↑↑ PTT ↑↑ PT F V assay	FFP
<b>Combined Factor V &amp; VIII Deficiency</b>	↓↓ F V ↓↓ F VIII	Mucocutaneous bleeding Hemarthrosis (rare)	↑↑ PTT ↑↑ PT FV, VIII assay	As ↓↓ FVIII
<b>Factor VII Deficiency</b>	↓↓ F VII (Stable factor)	Mucocutaneous bleeding, <b>spontaneous ICH</b>	↑↑ PT F VII assay	FFP ( $T_{1/2}$ = 2-4 hr) Recombinant FVII
<b>Factor X Deficiency</b>	↓↓ F X (Stuart-Prower)	Mucocutaneous bleeding	↑↑ PTT ↑↑ PT F X assay	FFP ( $T_{1/2}$ = 30 hrs)
<b>Factor II Deficiency</b>	↓↓ F II (Prothrombin)	Mucocutaneous bleeding	↑↑ PTT ↑↑ PT F II assay	FFP ( $T_{1/2}$ = 84 hrs) PCC
<b>Congenital afibrinogenemia</b>	↓↓ F I (Fibrinogen)	Bleeding	↑↑ PTT, ↑↑ PT ↑↑ TT, reptilase F I assay	<b>Cryo-precipitate</b> FFP ( $T_{1/2}$ = 2-4 days)
<b>Congenital dysfibrinogenemia</b>	Qualitative F I abnormality	Mild bleeding & thrombotic disorders	↑↑ PTT, ↑↑ PT ↑↑ TT, reptilase Normal FI %	<b>Cryo-precipitate</b> FFP ( $T_{1/2}$ = 2-4 days)
<b>Factor XIII Deficiency</b>	↓↓ F XIII (fibrin-stabilizing factor)	Mild bruising, <i>delayed separation of umbilical cord</i> , poor wound healing	<i>All routine tests are normal</i> (5M urea test) ↓↓ F XIII	<b>Cryo-precipitate</b> FFP ( $T_{1/2}$ = 5-7 days)
<b>Antiplasmin or PAI deficiency</b>	↓↓ PAI ↓↓ Antiplasmin	Mucocutaneous bleeding	↓↓ ELT Specific assay	FFP

### Acquired Coagulation disorders:

A) **Vitamin K deficiency:** [Vit. K dependent factors = II, VII, IX, X → ↑↑ PTT, ↑↑ PT]

Hemorrhagic disease of the NB, fat Malabsorption, prolonged use of broad-spectrum antibiotics

B) **Liver disease:** [All coagulation factors (except VIII) are synthesized in the liver → ↑↑ PT, PTT]

C) **DIC**

D) **Anticoagulants**

E) **Acquired Inhibitors of coagulation:**

- Idiopathic (?viral infection)
- Antiphospholipid Syndrome
- Coagulation factor therapy

# Von Willebrand Disease (Vascular hemophilia)

## Definition

It is the most common hereditary bleeding disorder (1% of population) due to deficiency (Type 1), absence (Type 3) or qualitative change in vWF (Type 2).

## Etiology

Genetic disease (AD)

vWF is an acute phase reactant (↑↑ in stress)

## Physiology of vWF

- ☑ **Structure:** large multimeric glycoprotein.
- ☑ **Synthesis:**
  - a. *Endothelial cells* → released into plasma & subendothelial matrix
  - b. *Megakaryocytes* → stored in platelets
- ☑ **Function:**
  - a. *Platelet adhesion:* through binding to platelet GPIb receptors → ↑↑ BT
  - b. *Carrier of VIII:C:* preventing its destruction by APC → ↑↑ PTT

## Clinical picture (♀ > ♂)

- Mucocutaneous bleeding (epistaxis, bleeding gums, post-tonsillectomy & post-tooth extraction bleeding, menorrhagia) & easy bruising
- Hemarthrosis is rare
- No bleeding with stressful procedures (childbirth, appendicectomy), Why?

## Investigations

vWF in stress

- Coagulation time & PTT: ↑↑, Bleeding time: ↑↑, PT & TT: normal
- Platelet count: ↓↓ in type 2B & in platelet type (pseudo-) vWD "indistinguishable"
- Platelet function (RIPA = ristocetin induced platelet-aggregation): impaired
- Factor VIII assay: may be ↓↓
- vWF antigen
- vWF activity (Ristocetin cofactor activity=vWF:RCO): patient plasma + normal platelet + ristocetin → if ↓↓ vWF → ↓↓ platelet aggregation

## Treatment

- Desmopressin (DDAVP): ↑↑ release of vWF from the endothelium → ↑↑ vWF & F VIII
- Cryoprecipitate (vWF & FVIII). Recombinant vWF may be available soon
- Antifibrinolytic agents (ε-aminocaproic acid): in dental bleeding & epistaxis

	Type 1	Type 3	Type 2A	Type 2B	Type 2M	Type 2N	PLT-vWD
vWF:Ag	↓↓	Absent	↓↓	↓↓	↓↓ or N	↓↓ or N	↓↓
vWF:RCO	↓↓	Absent	↓↓↓	↓↓	↓↓↓	↓↓ or N	↓↓
F VIII	↓↓ or N	↓↓↓	↓↓ or N	↓↓ or N	N	↓↓↓	↓↓ or N
RIBA	↓↓	Absent	↓↓	N	↓↓	N	N
LD RIPA	Absent	Absent	Absent	↑↑	Absent	Absent	↑↑
Platelet	N	N	N	↓↓	N	N	↓↓
DDAVP	Good	No	Poor	↓↓ PLT	Poor	Poor	↓↓ PLT
vWF conc	Good						↓↓ PLT
Rx	DDAVP vWF conc	vWF conc	vWF conc DDAVP	vWF conc	vWF conc	vWF conc DDAVP	PLT
Multimer	N but ↓↓	Absent	Abnormal	Abnormal	N but ↓↓	N but ↓↓	Abnormal

- ☑ Type 2A is caused by abnormal proteolysis of vWF → ↓↓ vWF:Ag & activity
- ☑ Type 2B is caused by hyperactive vWF → spontaneous binding to PLT → ↓↓ vWF & plt
- ☑ Type 2M is caused by ↓↓ platelet-binding function of vWF
- ☑ Type 2N is caused by ↓↓ F VIII-binding function of vWF (*autosomal hemophilia*)
- ☑ Platelet type vWD is caused by hyperactive platelet GPIb receptors (reverse of type

## Anticoagulants

### Indications

1. Deep venous thrombosis
2. Pulmonary embolism
3. Prosthetic valve
4. Extracorporeal circulation (HD, ECMO...)
5. DIC

### Contraindications

1. Active hemorrhage.
2. Bleeding tendency (ITP, hemophilia...)
3. Recent head trauma / surgery, ICH
4. Uncontrolled hypertension
5. Bacterial endocarditis

### **Low molecular weight heparin (LMW):**

Enoxaparin (Clexane).

#### **Dose** SC

Therapeutic: 1 mg/Kg/12 hrs

Prophylaxis: 0.5 mg/Kg/12 hrs

#### **Monitoring:** (Not PTT)

Factor X inhibition assay

LMW heparin level

**Advantages:** less bleeding complications

### Classifications

	Heparin	Oral anticoagulant (warfarin)
Source	Natural (GAG in mast cells)	Synthetic
Action	↑↑ AT III → # II, X, IX, XI Direct anti-thrombin	Competes with Vit.K. → # II, VII, IX, X, (Ptn C & S)
Route	Parenteral (IV, SC)	Orally
Onset	Immediate	Delayed 1-2 days (As it 1 <sup>st</sup> # Protein C & S)
Duration	4-6 hours	4-7 days
Dose	☒ 75-100 U/Kg/ 4-6 hrs or ☒ 20-30 U/Kg/hour	0.1-0.2 mg/Kg/day
Monitoring	PTT (1.5-2.5 times)	PT, INR (2-3)
Antidote	Protamine sulfate [1mg for 100U] FFP	Vitamin K (IV, SC or oral), Not IM FFP
Pregnancy	Safe	Teratogenic (cartilages)
Lactation	Safe	Safe

INR = International normalized ratio (N = 1): It allows comparison of PTs (reagents & instruments)

## Thrombolytic therapy

### Definition

Lysis of recently formed blood clots by enzymatic digestion through generation of plasmin (i.e., activation of endogenous plasminogen)

### Uses

Pulmonary embolism, DVT, arterial occlusion & vascular access patency (central catheters & arteriovenous fistulas). The clot should be relatively fresh (< 3-5 days)

### Drugs

Streptokinase, urokinase, tissue plasminogen activator (rTPA)

rTPA is more fibrin specific

### Monitoring

FDPs

### Side effects

Bleeding



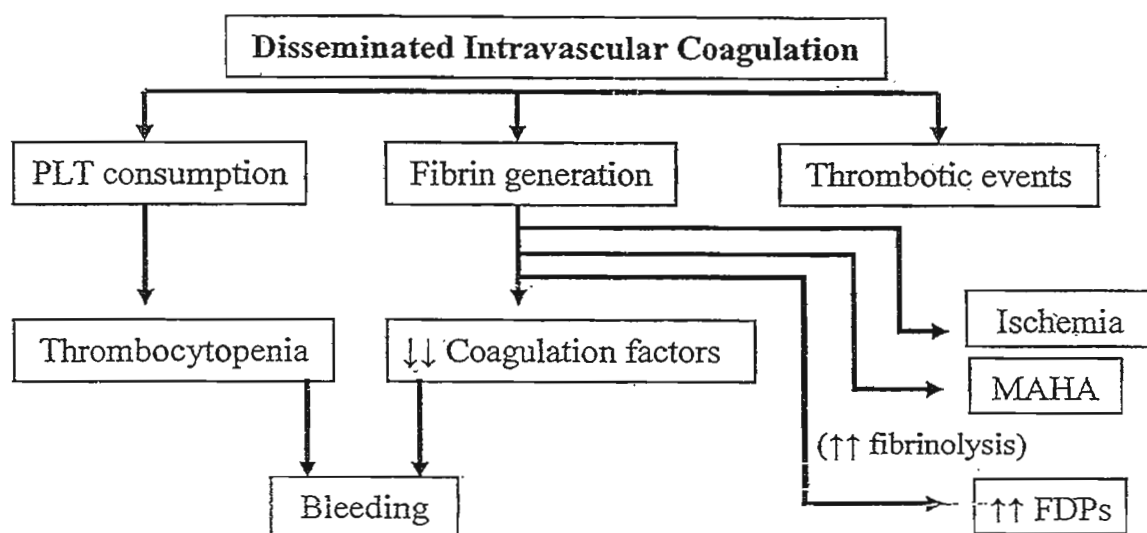
# Disseminated Intravascular Coagulation

## (Consumptive Coagulopathy)

### Definition

DIC is characterized by widespread intravascular coagulation leading to:

- Consumption of platelet & coagulation factors → bleeding
- Intravascular fibrin deposition
  - Tissue ischemia & necrosis
  - Microangiopathic hemolytic anemia (MAHA) & thrombocytopenia
- Activation of fibrinolysis → FDPs



### Etiology

1. **Septicemia:** (endotoxins, vascular injury, platelet injury, WBC activation, shock)  
Meningococcemia (Purpura fulminans), G-ve (Hemophilus), G+ve (GBS) sepsis
2. **Shock:** (hypotension, impaired tissue perfusion)
3. **Severe dehydration:** (vascular stasis)
4. **Snake & insect bites**
5. **Severe head injury:** (release of thromboplastin)
6. **Severe collagen-vascular disease, IBD**
7. **Burn, fracture (fat embolism), crush injury**
8. **Malignancy:** (Acute promyelocytic leukemia M3, neuroblastoma)
9. **MAHA:** (HUS, TTP, renal vein thrombosis)
10. **Hereditary thrombophilia** (AT III & protein C deficiency)
11. **Hyperthermia/ hypothermia**
12. **Incompatible blood transfusion**
13. **Acute graft rejection**
14. **Neonatal causes:** (PIH, RDS, NEC, GBS, Rh incompatibility)

### Clinical picture (Critically ill)

- Picture of the cause (sepsis, shock, GE...)
- Bleeding: Purpura, ecchymoses, puncture sites, internal hemorrhage
- Thrombosis: necrotic skin patches

## Investigations

- Coagulation time, PT, PTT, TT, bleeding time: prolonged
- Platelet count & Factors I, II, V, VIII: ↓↓
- CBC: fragmented RBCs (burr & helmet cells)
- FDPs & D-dimer: ↑↑

## Treatment

- Treatment of the cause** (sepsis, shock, dehydration)
- Replacement therapy:**
  - Whole blood (anemia)
  - FFP (coagulation factors)
  - Cryoprecipitate (fibrinogen)
  - Platelet (thrombocytopenia)
  - APC (in cases of sepsis & purpura fulminans)
- Heparin 75-100 U/Kg/ 4-6 hrs:** for thrombotic events & purpura fulminans
- Exchange transfusion:** for removal of toxins & addition of deficient factors

## Prognosis

Depends on the primary etiology

# Thrombotic Disorders

(Thrombophilia)

## A) Hereditary predisposition to thrombosis

### Etiology

#### 1. Protein C deficiency

Protein C is converted to activated protein C (APC) by thrombin-thrombomodulin complex  
APC → inactivates aV & aVIII (protein S acts as cofactor)

**C/P:**

- Neonatal period: purpura fulminans during 1<sup>st</sup> few hours (DD: neonatal sepsis)
- Later: thromboembolic disease (Less severe)

**Rx:**

- Neonatal period → FFP (source of protein C) or recombinant APC
- Later → long term warfarin therapy (INR= 3-5)

#### 2. Protein S deficiency

#### 3. Anti-thrombin III deficiency

**C/P:** Thromboembolic disease in adolescence

**Rx:** Heparin & warfarin

#### 4. Factor V Leiden (Resistance to APC): mutation of factor V gene → resistant aV

#### 5. Prothrombin gene mutation (G20210A): ↑↑ prothrombin synthesis

#### 6. Homocystinuria

## Diagnosis

- Clinical picture
- Family history
- Specific assay (protein C & S and Anti-thrombin III)
- Genetic analysis (factor V Leiden & prothrombin gene mutation)

### Other inherited thrombotic disorders:

1. Thrombomodulin deficiency
2. TPA deficiency
3. Dysfibrinogenemia
4. ↑↑ PAI-1
5. ↑↑ Levels of factors VIII, IX, X, XI

## B) Acquired predisposition to thrombosis

### Etiology

Antiphospholipid Abs react with components used in coagulation screening tests (↑↑ PTT)

#### 1. Antiphospholipid syndrome

Definition: It is systemic autoimmune disease characterized by:

- Thrombosis
- Recurrent fetal loss
- ↑↑ Level of antiphospholipid antibodies (lupus anticoagulant & anticardiolipin antibody)

Classification:

- a. Primary: isolated
- b. Secondary\* (underlying disease): SLE, infections

C/P: Thromboembolic disease

Investigations: ↑↑ PTT, specific assay

Rx: anticoagulant ± aspirin

#### 2. Nephrotic syndrome (Urinary loss of protein C& S and Anti-thrombin III)

#### 3. Congenital cyanotic heart disease (↑↑ Viscosity)

#### 4. Severe dehydration & shock

#### 5. DIC

#### 6. Prolonged immobilization (Fracture, postoperative)

#### 7. Sickle cell anemia (Stasis)

#### 8. Vessel injury (Catheters, trauma, thermal injury & IV contrast)

#### 9. Vasculitis (Kawasaki, SLE)

#### 10. Paroxysmal nocturnal hemoglobinuria

#### 11. TTP (Thrombotic thrombocytopenic purpura)

#### 12. Drugs: (oral contraceptives, estrogen, prednisone)

### Presentation

#### 1. Deep venous thrombosis (Pain, swelling & tender calf muscles)

Rx: Rest, elevation, heparin followed by warfarin

#### 2. Arterial thrombosis

Rx: Thrombolytic therapy or surgical thrombectomy

#### 3. Stroke (Rapidly developing signs of focal disturbance of cerebral function with symptoms lasting > 24 hrs with no apparent cause other than of vascular origin)

#### 4. Pulmonary embolism

Rx: Heparin or thrombolytic therapy, intracaval filter, pulmonary embolectomy

# Purpura

## Definition

It is small hemorrhage into the superficial layers of the skin producing areas of purple discoloration which do not blanch on pressure. Minute spots of 1-2 mm are called petichiae and larger areas of 1-2 cm are called ecchymoses

## Classification

A) **Non-thrombocytopenic purpura** (Vascular or platelet dysfunction)

B) **Thrombocytopenic purpura** (Platelet count  $< 150,000/\text{mm}^3$ )

### A) Non-thrombocytopenic Purpura

#### 1. Vascular

Congenital	Acquired
<ol style="list-style-type: none"> <li>1. Ehler-Danlos syndrome <ul style="list-style-type: none"> <li>▪ Hyperelasticity of the skin</li> <li>▪ Hyperlaxity of joints</li> </ul> </li> <li>2. Marfan syndrome</li> <li>3. Osteogenesis imperfecta</li> <li>4. Ataxia telangiectasia</li> </ol>	<ol style="list-style-type: none"> <li>1. Immune <ul style="list-style-type: none"> <li>▪ Henoch-Schonlein vasculitis</li> <li>▪ SLE, PAN</li> </ul> </li> <li>2. Infection <ul style="list-style-type: none"> <li>▪ Meningococemia</li> <li>▪ Infective endocarditis</li> </ul> </li> <li>3. Steroids (Cushing' syndrome) <ul style="list-style-type: none"> <li>▪ Exogenous</li> <li>▪ Endogenous</li> </ul> </li> <li>4. Scurvy</li> </ol>

#### 2. Platelet dysfunction (Thrombocytopathy)

Congenital	Acquired
<p><b>A) Defects of adhesion</b></p> <ul style="list-style-type: none"> <li>▪ vWD</li> <li>▪ Bernard-Soulier (AR)</li> </ul> <p><u>Defect:</u> <math>\downarrow\downarrow</math> platelet GPIb receptors (vWF)</p> <p><u>Features:</u> <b>Giant platelet</b> Thrombocytopenia <math>\downarrow\downarrow</math> RIPA</p> <p><b>B) Defects of aggregation (Glanzmann disease)</b></p> <p><u>Defect:</u> <math>\downarrow\downarrow</math> Platelet fibrinogen receptors</p> <p><u>Features:</u> Normal platelet count Normal adhesion (normal vWF) Defective aggregation</p> <p><b>C) Defects of platelet secretion</b></p> <ul style="list-style-type: none"> <li>▪ Dense body deficiency (<math>\downarrow\downarrow</math> ADP)</li> <li>▪ Gray platelet <math>\\$</math> (<math>\downarrow\downarrow</math> Plt <math>\alpha</math> granules)</li> </ul> <p><b>D) <math>\downarrow\downarrow</math> PF3</b></p>	<ol style="list-style-type: none"> <li>1. Drug induced (Not dose-related) (# cyclo-oxygenase enzyme) <ul style="list-style-type: none"> <li>▪ Aspirin</li> <li>▪ NSAIDs (indomethacin, ibuprofen...)</li> <li>▪ Valproate</li> </ul> </li> <li>2. Uremia (uremic toxins) Bleeding is an indication of dialysis Dialysis can correct this defect</li> <li>3. Systemic diseases <ul style="list-style-type: none"> <li>▪ Chronic ITP</li> <li>▪ SLE</li> <li>▪ Leukemia</li> <li>▪ Congenital cyanotic HD</li> <li>▪ Liver cell failure</li> </ul> </li> </ol> <div style="text-align: center;"> <p>Arachidonic acid</p> <p><math>\downarrow</math> <i>cyclo-oxygenase</i></p> <p>Thromboxane <math>A_2</math> (<math>\uparrow\uparrow</math> aggregation)</p> </div>
<p><b>Rx:</b></p> <ol style="list-style-type: none"> <li>a. Desmopressin (DDAVP) "vWF"</li> <li>b. Platelet transfusion</li> <li>c. Stem cell transplantation</li> </ol>	

- radiation or INF- $\alpha_2$  (anti-angiogenic)
- 2. Bernard-Soulier \$ (Giant platelets)
- 3. Wiskott-Aldrich \$

- Drug mediated ( $\alpha$ -methyl.dopa)
- Mechanism:* Drug acts as a **hapten**
- B) Non-immune**
  - Hypersplenism (sequestration)
  - Infection (sepsis)
  - Microangiopathic diseases (HUS, TTP, renal vein thrombosis, DIC)

**Immune neonatal thrombocytopenia:** (Good prognosis 2-4 months: Why?)

#### Causes

1. Maternal autoantibodies (Transplacental passage of maternal Ab)

- |                 |  |
|-----------------|--|
| a. SLE          | } ↓↓ Maternal platelet count<br>Milder C/P than NATP<br>Rx: maternal steroid, IVIG |
| b. ITP          |  |
| c. Drug induced |  |

2. Neonatal alloimmune thrombocytopenia (NATP) "Rh incompatibility analog"

**Cause:** Maternal allantibodies against fetal platelet antigen acquired from the father  
The 1<sup>st</sup> baby is usually affected

**C/P:** Petichiae, mucocutaneous hemorrhage, ICH

**Diagnosis** Normal maternal platelet count

Maternal Ab against father's platelets

**Monitoring** of fetal platelet count (percutaneous umbilical blood sampling = PUBS)  
± platelet transfusion

**Rx** Antenatal IVIG to the mother (2<sup>nd</sup> trimester) → Elective CS

Neonate Blood transfusion, washed platelet transfusion (from the mother)  
IVIG, steroid

- Coombs' test (Evans syndrome)
- ANA, ESR: ITP may be the 1<sup>st</sup> manifestation of collagen vascular diseases (SLE)

#### Treatment

*There is No general agreement about management of ITP*

*Platelet transfusion is contraindicated unless life-threatening bleeding occurs*

*ICH remains a rare complication*

*There is no relationship between platelet count & severity of ITP*

**A) Mild cases (cutaneous):** Avoid trauma & salicylates with close observation & F/U

#### **B) Treatment options:**

1. **IVIG:** 400 mg/Kg/day for 5 days Or 0.8-1 g/Kg/day for 1-2 days

*Advantages:* Rapid ↑↑ platelet count

*Disadvantages:* Expensive, ↑↑ aseptic meningitis

2. **Prednisone:** 2 mg/Kg/day for 2-3 weeks or until platelet  $>20,000/\text{mm}^3$  with rapid tapering (guided by clinical & lab response)

3. **IV anti-D antibodies:**

*Requirements:* Rh +ve patient with Hb  $>10\text{g}\%$

*Mechanism:* mild hemolytic anemia → Saturation of splenic Fc receptors with RBC-Ab complexes → ↓↓ platelet destruction

4. **Splenectomy** (Site of Ab production & platelet destruction)

*Indications:*

- Severe chronic ITP in older child  $>4$  years
- Acute ITP with life-threatening bleeding not corrected by steroids, IVIG or platelet transfusion

5. **Platelet transfusion** (When?)

### C) Chronic ITP (persistent thrombocytopenia > 6 months)

- Exclude other causes e.g., SLE, vWD 2B, Wiskott-Aldrich \$
- Steroids, other immunosuppressives (e.g., azathioprine, cyclosporine, vincristine)
- IVIG
- Anti-D therapy
- Splenectomy

## Thrombocytosis

### Definition

Platelet count > 750,000/ mm<sup>3</sup>

### Etiology

#### A) Primary (= Myeloproliferative syndrome)

Overproduction of platelets in cases of polycythemia vera, chronic myeloid leukemia (CML) & essential thrombocythemia

#### B) Secondary (Reactive):

1. Iron deficiency (EPO has some structural homology with thrombopoietin)
2. Acute hemorrhage
3. Chronic hemolytic anemia
4. Postsplenectomy (& asplenia) [1/3 platelets are sequestered in the spleen]
5. Collagen-vascular diseases (Kawasaki, systemic-onset JRA, PAN, IBD)
6. Response to exercise, trauma & surgery
7. Response to drugs (adrenaline)
8. Recovery from thrombocytopenia
9. Recovery from suppressive drugs
10. Nephrotic syndrome

### Clinical picture

- *Asymptomatic* in the majority of patients
- *Thrombotic* manifestations (e.g., venous thrombosis, pulmonary embolism...)

### Investigations

- CBC: ↑↑ platelet count
- Platelet function: normal

### Treatment

- Asymptomatic: No Rx
- Thrombotic manifestations: Anti-platelet therapy
  - ☒ Acetyl salicylic acid (Aspirin) # cyclo-oxygenase enzyme: 80-160 mg/day
  - ☒ Dipyridamol
- Plateletpheresis (thrombocytapheresis)

# Anemia

## Definition

It is reduction in hemoglobin concentration or hematocrit below normal for age & sex. More accurately, it is defined as reduction in red cell mass  $\rightarrow$   $\downarrow\downarrow$  O<sub>2</sub> delivery to tissues

## Pathophysiology

1.  $\uparrow\uparrow$  Cardiac output ( $\uparrow\uparrow$  HR,  $\uparrow\uparrow$  VR,  $\uparrow\uparrow$  SV)  $\rightarrow$  Hyperdynamic circulation
2.  $\uparrow\uparrow$  Pulmonary function (tachypnea)
3.  $\uparrow\uparrow$  O<sub>2</sub> delivery to tissues "shift to right" due to  $\uparrow\uparrow$  2,3 DPG (2,3 diphosphoglycerate)
4.  $\uparrow\uparrow$  Erythropoietin (renal hypoxia)  $\rightarrow$  BM hyperactivity (6-8 folds)
5.  $\uparrow\uparrow$  Plasma volume
6. Redistribution of blood to the vital organs (brain & heart)

## Clinical picture (depends on severity & rate of development)

### A) Symptoms

- Fatigue
- CVS: exertional dyspnea, palpitation, HF
- CNS: headache, tinnitus, syncope, lack of concentration
- Renal: polyuria (mild proteinuria)

### B) Signs

- Pallor
- Hyperdynamic circulation: tachycardia, big pulse volume,  $\uparrow\uparrow$  heart sounds, hemic murmurs & HF

### C) Picture of the cause

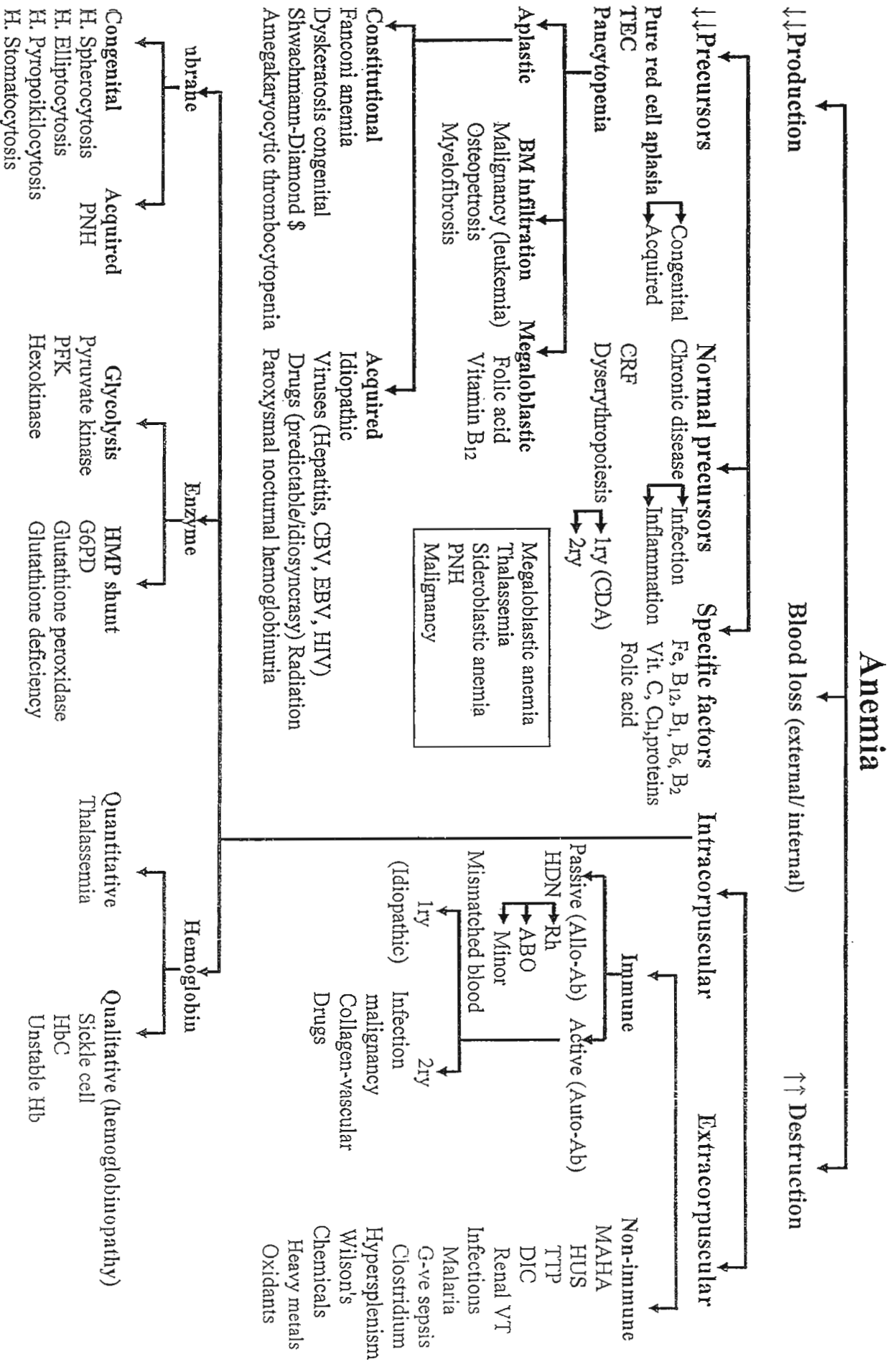
- Iron deficiency anemia: koilonychia (spoon-shaped nails)
- Megaloblastic anemia (B<sub>12</sub>): neurological manifestations
- Hemolytic anemia: jaundice, organomegaly
- Aplastic anemia: bleeding & fever
- Malignancy (leukemia): bleeding, fever, HSM & lymphadenopathy

## Classification

### A) Morphological (according to MCV)

Microcytic (MCV < 75 fl)	Normocytic (MCV = 75-90 fl)	Macrocytic (MCV > 100 fl)
Iron deficiency anemia	Hemorrhage (internal/external)	Normal newborn
$\beta$ -Thalassemia trait	Hemolysis (membrane/enzyme)	Folic acid & B <sub>12</sub> deficiency
$\beta$ -Thalassemia major	Bone marrow infiltration	$\uparrow\uparrow$ Erythropoiesis ( $\uparrow\uparrow$ Retics)
$\alpha$ -Thalassemia trait	Renal failure	Diamond-Blackfan & Pearson
HbH disease ( $\beta_4$ )	Collagen-vascular diseases	CDA
Chronic disease (infection)	Chronic disease (infection)	Aplastic anemia (cons. /acq.)
Lead poisoning	Hypersplenism	Myelodysplastic syndromes
Sideroblastic anemia	Sequestration	Orotic aciduria
Atransferrinemia		Lesch-Nyhan syndrome
Copper deficiency		Thiamine-responsive megaloblastic anemia
Malabsorption (Celiac)		Liver disease-Hypothyroidism
Iron malabsorption		Vitamin B <sub>6</sub> deficiency

### B) Etiological





## Pure Red Cell Anemia

### Definition

It is deficiency or absence of red cell precursors in an otherwise normal bone marrow

### Classification

- A) Congenital pure red cell anemia (Diamond-Blackfan \$)
- B) Acquired pure red cell anemia

### Congenital Pure Red Cell Anemia (Congenital hypoplastic anemia-Diamond-Blackfan \$)

#### Etiology

- Sporadic: the majority
- Inherited: 15% (AD, AR)

#### Clinical picture (Onset = usually in 1<sup>st</sup> 3 months)

- *Pallor*
- *Hydrops fetalis* (Fetal anemia)
- *Physical anomalies*: short stature, triphalangeal thumb, UL & cardiac anomalies
- *Transfusion dependent* → hemosiderosis → HSM "Iron overload"
- *Spontaneous remission* occurs in 20 % of patients
- *Premalignant condition* (AML)

#### Investigations

- CBC: anemia (↓↓ Hb %), **macrocytic** (MCV ↑↑)  
Platelet & WBC: initially normal (↓↓ with hypersplenism)
- ↓↓ Reticulocytic count
- ↑↑ Serum iron
- ↑↑ Erythropoietin
- ↑↑ Hb F (hematologic stress)
- Normal RBC survival
- ↑↑ RBC adenosine deaminase activity (ADA)
- Normal chromosomal studies (DD: Fanconi anemia)
- BM examination (aspirate/ biopsy): ↓↓ red cell precursors (↑↑ Apoptosis)  
Normal myeloid & megakaryocytic series  
↑↑ M/E ratio > 10

Normal M/E ratio  
2:1- 4:1

#### Treatment

- Chronic transfusion therapy + iron chelating therapy (Deferoxamine or Deferiprone)
- Prednisone (2 mg/Kg/day): monitored with Hb % & Retics (response rate = 75 %)
- Other immunosuppressive agents (cyclophosphamide, cyclosporin)
- Hematopoietic stem cell transplantation (HLA-matched donor)

#### Complications

- Hemosiderosis
- Malignancy
- Steroid & immunosuppressive toxicity
- Complication of HSCT

#### Pearson marrow-pancreas \$

##### Features:

1. Congenital hypoplastic anemia

BM → Vacuolization of erythroid & myeloid precursors

Ringed sideroblasts (It is a form of congenital sideroblastic anemia)

2. Pancreas: IDDM, exocrine pancreatic dysfunction (FTT, Malabsorption & chronic diarrhea)
3. Others: Muscle & neurological impairment

**CBC:** anemia (macrocytic), neutropenia & thrombocytopenia    **Rx:** Blood transfusion

**Etiology:** mt DNA deletion

**Pathology:** Pancreatic fibrosis & BM changes

## Acquired Pure Red Cell Anemia

### A) Transient Erythroblastopenia of Childhood (TEC) (most common)

It is acquired red cell aplasia due to transient **immunologic suppression of erythropoiesis** usually following viral infection (Not Parvovirus B 19)

	Diamond-Blackfan S	TEC
Frequency	Rare	More common
Age at diagnosis	90 % by 1 <sup>st</sup> year	6 months-3 yrs
Etiology	Genetic	Acquired (viral/ idiopathic)
Congenital anomalies	Present (triphalangeal thumb, UL, cardiac, renal)	Absent
HB %	3-4 %	3-9 %
Transfusion dependence	Transfusion or steroid dependent	Not
MCV	Macrocytic > 100 fL	Normocytic
Hb F	↑↑	Normal
RBC ADA activity	↑↑	Normal
Treatment	Steroids, Packed RBC, HSCT	Packed RBC if required
Prognosis	Spontaneous recovery (only 20 %)	Spontaneous recovery (wks-months)

### B) Red cell aplasia associated with chronic hemolysis

Parvovirus B-19 is cytotoxic to RBC precursors → transient ↓↓ erythropoiesis < 2 wks  
It is self-limited condition; unnoticed in normal individuals (RBC life span=110-120d)  
It causes aplastic crisis in patients with chronic hemolytic (short RBC life span)

### C) Red cell aplasia associated with immunodeficiency (Congenital/acquired)

Due to persistent Parvovirus B 19 infection

**Diagnosis:** Serology (IgM), viral DNA (PCR), Prenatal (viral DNA in fetal blood)

**Rx:** IVIG

### D) Red cell aplasia associated with hydrops (Non-immune hydrops)

It is due transplacental infection with Parvovirus B 19

### E) Red cell aplasia associated with other diseases (Ab mediated)

SLE, CLL, lymphoma

### F) Red cell anemia associated with some drugs (e.g., chloramphenicol)

• **NB:** Hematological toxicity of chloramphenicol: (2 effects)

	Pancytopenia	Erythroid depression
Dose	Idiosyncrasy (not dose-related)	Dose-related
Genetics	Genetic predisposition	No
Route	Follows oral administration	Any
Mechanism	Formation of toxic metabolite by intestinal bacteria	Inhibition of iron uptake by normoblasts Inhibition of iron incorporation into Hb

## Dyserythropoiesis (Ineffective erythropoiesis)

### Definition

It is erythroid hyperplasia with production of defective erythrocytes which are destroyed within the **bone marrow** or immediately after release into the **peripheral blood**. There is marked discrepancy between the BM picture "hyperplasia" & periphery "anemia"

### Classification

A) **Congenital dyserythropoietic anemia**

B) **Secondary dyserythropoietic anemia** (Thalassemia, megaloblastic, sideroblastic, PNH, malignancy)

## Congenital Dyserythropoietic Anemia

### Definition

It is a rare disorder characterized by ineffective erythropoiesis, macrocytic anemia & unique BM "RBC precursor" abnormalities (multinuclearity & abnormal chromatin patterns)

### Etiology (Genetic AR /AD)

Impaired membrane protein glycosylation

### Clinical picture (Onset = may present in the neonatal period)

- Variable degrees of anemia
- Intermittent jaundice
- Splenomegaly

**Immunodeficiency**  
Congenital/acquired

### Investigations

- CBC: anemia (↓↓ Hb %), macrocytic (MCV ↑↑). Platelet & WBC: normal
  - ↓↓ Reticulocytic count
  - ↑↑ Serum iron (Ineffective erythropoiesis)
  - ↓↓ RBC survival
  - ↑↑ Serum bilirubin (indirect)
  - BM examination (aspirate/ biopsy): Erythroid hyperplasia (↑↑ red cell precursors)  
Normal myeloid & megakaryocytic series  
↓↓ M/E ratio
- DD: Hemolytic anemia but ↓↓ Retics

	CDA Type I	CDA Type II*	CDA Type III
<b>Inheritance</b>	AR	AR	AD
<b>Chromosome</b>	15	20	15
<b>BM erythroblast</b>	Binuclear Megaloblastic	Multinuclear (2-7) Normoblastic	Multinuclear (up to 12) Megaloblastic
<b>Serology</b>	-Ve	+Ve	-Ve
<b>Ham test</b>	-Ve	+Ve	-Ve
<b>RBC i antigen agglutination</b>	Normal	Strong	Normal
<b>Treatment</b>	Blood transfusion + iron chelation ± splenectomy		
	INF-α	-	-

Acidified serum test (Ham test): patient's RBCs are lysed by acidified serum from normal individuals but not by the patient's own acidified serum (DD: PNH)

CDA type II is called **HEMPAS** (= **H**ereditary **E**rythroblastic **M**ultinuclearity with **P**ositive **A**cidified Serum test)

## Anemia of Chronic Disease

### Etiology

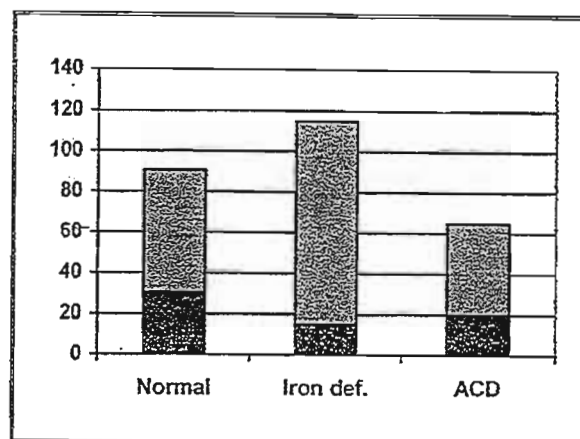
- Chronic **infection**: Bronchiectasis, TB, osteomyelitis
- Chronic **inflammation**: SLE, JRA, IBD
- **Malignancy**

### Pathogenesis

- Hypoactive BM
- $\downarrow\downarrow$  Erythropoietin (*relative to degree of anemia*)
- $\downarrow\downarrow$  Iron utilization
- $\downarrow\downarrow$  RBC life span (hemolysis by RES)
- Release of cytokine :  $\text{INF-}\beta$ ,  $\text{INF-}\gamma$ , TNF

### Clinical picture

- Anemia
- Picture of the cause



### Investigations

- CBC: Normocytic normochromic anemia (may micro- hypo-), leukocytosis
- $\downarrow\downarrow$  Reticulocytic count
- $\downarrow\downarrow$  Serum iron,  $\downarrow\downarrow$  TIBC (Total iron binding capacity),  $\downarrow\downarrow$  iron saturation,  $\uparrow\uparrow$  Serum ferritin
- $\downarrow\downarrow$  RBC survival
- $\uparrow\uparrow$  Free erythrocyte-protoporphyrin (FEP):  $\downarrow\downarrow$  iron utilization  $\rightarrow$   $\downarrow\downarrow$  Heme synthesis
- BM examination (aspirate/ biopsy):  $\uparrow\uparrow$  hemosiderin

### Treatment

- Treatment of the cause
- Recombinant human erythropoietin [r-HuEPO]

## Anemia of CRF

### Pathogenesis

1.  $\downarrow\downarrow$  Erythropoietin (most important)
2.  $\downarrow\downarrow$  iron utilization
3.  $\downarrow\downarrow$  RBC life span (# of Na-K ATPase  $\rightarrow$  Hemolysis)
4.  $\downarrow\downarrow$  intake: anorexia & vomiting
5. Dilutional anemia
6. Bleeding tendency (Thromocytopathy)
7. Bleeding: sampling, insertion of VA (Central catheters)
8. VA-related complications
9. Residual blood in HD machine circuits
10. Loss of folic acid in HD treatment (dialyzable)

Benefits	Complication
Avoid blood transfusions	Iron deficiency
$\downarrow\downarrow$ sensitization to HLA antigens	Hypertension
$\downarrow\downarrow$ exposure to infectious disease	Seizures
$\uparrow\uparrow$ appetite	Pure red cell aplasia
$\uparrow\uparrow$ exercise tolerance, activity	Clotting of vascular access

### Clinical picture& Investigations

### Treatment

- Recombinant human erythropoietin [r-HuEPO]: 50-100 units/kg SC 1-3 times/ wk  
It is indicated when Hb < 10g%
- Packed RBC ( $\downarrow\downarrow$  success of renal transplantation due to sensitization)
- Dialysis or renal transplantation

# Megaloblastic Anemia

## Definition

Anemia due to impairment of DNA synthesis leading to delayed cell division & cellular gigantism. It is characterized by BM megaloblasts & blood macrocytes

## Etiology

> 90 % are due to folic or vitamin B<sub>12</sub> deficiency

## Physiology

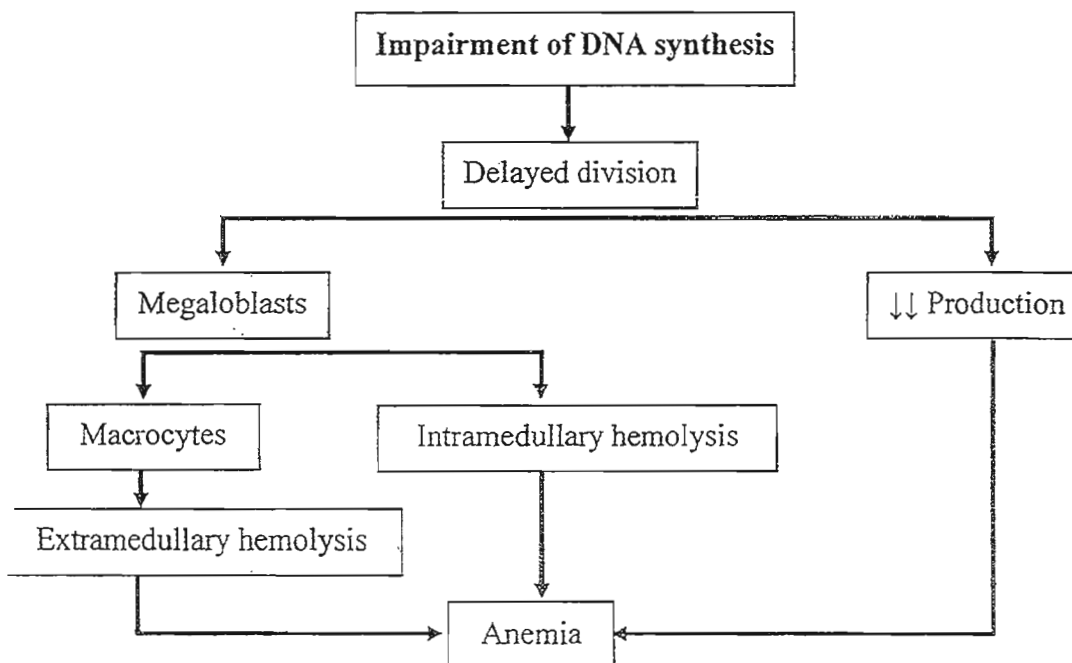
	Vitamin B <sub>12</sub>	Folic acid
<b>Source</b>	Animal origin (milk, meat)	Plant (green leaves) & animal (liver)
<b>Requirements</b>	2.5 µg / day (Stores are sufficient for 3-5 yrs)	25-35 µg / day (↑↑ in preterm, pregnancy, CHA)
<b>Absorption</b>	1. Gastric parietal cell → Intrinsic factor → IF-B <sub>12</sub> complex 2. Binding to specific receptors 3. Absorption in <b>terminal ileum</b> (by endocytosis)	Proximal jejunum
<b>Transport</b>	Transcobalamin I, II, III	Plasma proteins
<b>Functions</b>	Two coenzyme forms: 1. <i>Adenosylcobalamin</i> M.M.CoA → Succinyl CoA 2. <i>Methylcobalamin</i> Homocysteine → Methionine 3. <i>Regeneration of THF</i>	Folic → DHF → THF (active form) [* = Dihydrofolate reductase] 1. Biosynthesis of DNA 2. Formation of methionine Homocysteine $\xrightarrow[\text{THF}]{\text{B}_{12}}$ Methionine Methyl THF

M.M.CoA = Methylmalonyl CoA

THF = Tetrahydrofolic acid

## Pathophysiology (Nuclear-cytoplasmic dissociation)

- Impairment of DNA synthesis leading to delayed cell division & nuclear maturation
- RNA & protein synthesis in the cytoplasm are **not** affected
- Megaloblastic changes occur in all cell precursors
- Ineffective erythropoiesis, leukopoiesis & thrombopoiesis (due to lack of DNA repair)



## Etiology

Deficiency of Vitamin B <sub>12</sub>	Deficiency of Folic acid
<b>↓↓ Intake</b> Vegetarians-malnutrition	<b>↓↓ Intake</b> Goat milk-↓↓ vegetable intake- malnutrition
<b>↓↓ Absorption</b> <b>a. ↓↓ Intrinsic factor (IF)</b> <ul style="list-style-type: none"> <li>• Congenital pernicious anemia (AR)</li> </ul> Absence of IF or biologically inactive IF Normal HCl secretion by parietal cells <ul style="list-style-type: none"> <li>• Juvenile pernicious anemia</li> </ul> Ab against IF & parietal cells Associated with: HAM \$, thyroid disease... <ul style="list-style-type: none"> <li>• Gastrectomy</li> <li>• Caustics</li> </ul> <b>b. Failure of intestinal absorption</b> <ul style="list-style-type: none"> <li>• Specific Vit. B<sub>12</sub> malabsorption</li> </ul> Defective receptors for IF-B <sub>12</sub> complex <ul style="list-style-type: none"> <li>• Generalized malabsorption</li> <li>• Terminal ileum disease</li> </ul> NEC, Crohn disease, TB enteritis, resection <ul style="list-style-type: none"> <li>• Bacterial overgrowth</li> <li>• Diphyllobothrium latum</li> </ul>	<b>↓↓ Absorption</b> <b>a. Generalized malabsorption</b> Celiac, short bowel... <b>b. Specific folic acid malabsorption</b> Associated with defective transport of folic acid to CNS [Megaloblastic anemia & MR]
	<b>↑↑ Requirements</b> <ul style="list-style-type: none"> <li>▪ Premature infants (50-200 µg/day)</li> <li>▪ Pregnancy &amp; lactation (400 µg/day)</li> <li>▪ Chronic hemolytic anemia</li> <li>▪ HD</li> <li>▪ Malignancy</li> <li>▪ Extensive skin disease (psoriasis)</li> </ul>
<b>↓↓ Transport</b> Congenital absence of transcobalamin II	<b>Disorders of folic acid metabolism</b> <ul style="list-style-type: none"> <li>▪ Congenital Dihydrofolate reductase ↓↓</li> <li>▪ Dihydrofolate reductase inhibition [Trimethoprim, Methotrexate, Pyrimethamine]</li> <li>▪ Anticonvulsants (phenytoin, phenobarb)</li> </ul>
<b>Disorders of Vit. B<sub>12</sub> metabolism</b> Deficiency of methyl- & adenosylcobalamin	

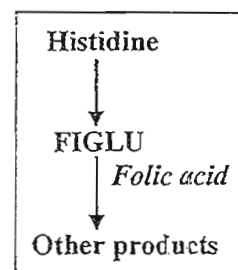
## Clinical picture

- A) **Hematological:** anemia, pancytopenia (infection & bleeding)  
 B) **GIT:** glossitis & diarrhea  
 C) **Neurological:** peripheral neuritis, neuropsychiatric changes & subacute combined degeneration of the spinal cord
- Posterior column: deep sensory loss, sensory ataxia
  - Pyramidal tract: +ve Babinski sign, clonus

**Neurological manifestations only in vitamin B<sub>12</sub> deficiency**

## Investigations

- CBC: RBC → Macrocytic normochromic anemia, ↓↓ Retic  
 WBC → Leukopenia, hypersegmented PNLs (shift to Rt)  
 PLT → Thrombocytopenia, giant platelets
- ↑↑ Serum iron (Ineffective erythropoiesis)
- ↓↓ RBC survival
- ↑↑ Serum bilirubin (indirect)
- ↑↑ LDH
- BM examination (aspirate/ biopsy): hypercellular megaloblastic BM
- Measurement of serum folic acid & vitamin B<sub>12</sub>
- Urinary excretion of methylmalonic acid (↑↑ with vitamin B<sub>12</sub> deficiency)
- FIGLU test (formiminoglutamic acid): ↑↑ urinary excretion of Figlu after oral histidine indicates folic acid deficiency (*folic acid is important for Figlu metabolism*)
- Schilling test:



- ☒ IM vitamin B<sub>12</sub> (1 mg) to **saturate** body stores & transcobalamins
- ☒ **Oral radioactive** vitamin B<sub>12</sub> (1 µg)
- ☒ **Urine** is collected to measure excreted vitamin B<sub>12</sub>
- ☒ Normally, **10-30 %** of the absorbed oral dose is excreted in urine
- ☒ ↓↓ excretion indicates ↓↓ absorption
- ☒ Give **oral IF** with radioactive vitamin B<sub>12</sub>, if ↑↑ excretion → IF deficiency
- ☒ Failure of ↑↑ excretion (after IF) indicates intestinal cause of malabsorption

### Treatment

*Vitamin B<sub>12</sub> deficiency should be **excluded** before administration of folic acid since it may **aggravate** neurological manifestations*

- Vitamin B<sub>12</sub> deficiency: IM (1000 µg) monthly [Depovit B<sub>12</sub>]
- Folic acid deficiency: 0.5-1 mg/day start with low dose [Folic acid tablet]

## Other Causes of Megaloblastic Anemia

### **A) Orotic Aciduria (AR)**

**Cause:** Deficiency of orotic phosphoribosyltransferase (OPRTase)

**C/P:** Megaloblastic anemia, developmental delay (motor & mental)

**Diagnosis:** ↑↑ excretion of orotic acid (& crystalluria)

**Rx:** Uridine

### **B) Lesch-Nyhan syndrome (XL-R)**

**Cause:** Deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRase)

**C/P:** Megaloblastic anemia, developmental delay (motor & mental), self-mutilation

**Diagnosis:** ↑↑ serum uric acid

### **C) Thiamine-responsive megaloblastic anemia (AR)**

**Cause:** Deficiency of thiamine

**C/P:** Megaloblastic anemia, cardiomyopathy, deafness, optic nerve atrophy

**Rx:** Thiamine

### **Iron metabolism** (*Iron hemostasis is regulated mainly by absorption rather than excretion*)

**Sources:** organ meat, egg yolk, muscle meat, whole cereals

**Requirements:** 1-1.5 mg/day (diet should contain 10-15 mg/day, as normally 10-15 % is absorbed)

**Absorption:** in the duodenum & upper jejunum, in the ferrous state (Fe<sup>++</sup>) "ascorbic acid"

Cu is important for iron absorption & mobilization

#### **Factors affecting iron absorption:**

- Needs of the body: enterocytes contain ferritin & transferrin [mucosal-block]
  - ↓↓ Iron stores → ↓↓ apoferritin, ↑↑ apotransferrin → ↑↑ iron absorption
  - ↑↑ Iron stores → ↑↑ apoferritin, ↓↓ apotransferrin → ↓↓ iron absorption "Fe trap & slough"
- Rate of erythropoiesis: hemolysis & hge are associated with ↑↑ iron absorption
- Dietary phytic acid, PO<sub>4</sub>, oxalate, FA, tannic acid → ↓↓ iron absorption
- Ascorbic acid → ↑↑ iron absorption

**Excretion:** mainly in stools, urine, breast feeding & menstruation (0.5-1 mg/day)

# Iron Deficiency Anemia

## Definition

It is the **most common** cause of anemia

### Iron distribution

**A) Functional:** Hemoglobin, myoglobin, enzymes (catalase, cytochrome oxidase P<sub>450</sub>, monoamine oxidase = MAO)

### B) Nonfunctional:

- Ferritin (main storage form - **reliable** index of iron storage)
- Hemosiderin (iron storage form - not present in plasma)
- Transferrin: (transport form in the plasma)

Normally, transferrin can carry 250-400 µg of iron/ dL (= **TIBC**)

Normal serum iron = 40-140 µg/dL

Normally, 30 % of TIBC is saturated

**Hemosiderosis:** accumulation of hemosiderin in the cells of RES with mild tissue damage

**Hemochromatosis:** hemosiderosis with injury of **parenchymal** cells. (liver, pancreas, heart...)

## Etiology

### 1. ↓↓ Intake

Cow's milk, exclusive breast milk or powder milk without supplementation

### 2. ↓↓ Absorption (e.g., celiac disease...)

### 3. ↑↑ Loss of iron (chronic blood loss)

- |                                     |                                  |
|-------------------------------------|----------------------------------|
| ▪ Parasitic: Ankylostoma (hookworm) | ▪ Cow's milk protein intolerance |
| ▪ Sampling                          | ▪ Peptic ulcer & varices         |
| ▪ Meckel's diverticulum             | ▪ Polyps & hemangiomas           |
| ▪ IBD                               | ▪ Pulmonary hemosiderosis        |

## Clinical picture (Onset ≈ 6 months)

### A) Hematological: anemia

### B) Neurological:

- ↓↓ alertness, attention span & intellectual functions
- Stroke (RBC wall rigidity)
- Pica (ingestion of non-nutrient materials)
- ?? ↑↑ frequency of breath-holding attacks

### C) Epithelial changes

- Nails: thin, lusterless, brittle, longitudinal ridges, koilonychia (spoon-shaped)
- Glossitis & angular stomatitis
- Hair: dry & brittle

### D) Splenomegaly (10 %)

Preterm require iron supplementation once they are on full enteral feeds

## Investigations

- CBC: RBC → Microcytic hypochromic anemia (↓↓ MCV & MCH), ↑↑ RDW, Anisocytosis, poikilocytosis, Retic (normal or ↓↓ but ↑↑ after Rx)
- WBC → Normal (eosinophilia may be present. Why?)
- PLT → Thrombocytosis
- ↓↓ Serum iron with ↑↑ TIBC, ↓↓ iron saturation, ↑↑ TfR
- ↓↓ Serum ferritin < 10 ng/ml (more accurate) →
- ↑↑ Free erythrocyte protoporphyrin (FEP).
- BM examination (aspirate/ biopsy): Hypercellular (erythroid hyperplasia)
- Investigation of the cause (e.g., Stool analysis, BAL, normal Hb electrophoresis...)

The gold standard in documenting total iron stores is BM aspirate



## Treatment

**Iron therapy should be continued for at least 3 months**

1. Treatment of the cause
2. Dietary supplementation
3. Iron therapy (6 mg elemental iron / Kg / day)
  - a. Oral (ferrous gluconate or ferrous sulfate)  
Give in 3 divided doses in between meals (Vitamin C helps iron absorption)
  - b. Parenteral (Iron dextran)  
Indicated in cases of malabsorption, intolerance to oral iron & non-compliance  
Not more rapid. Not more effective

### Response to iron therapy

Time after Iron Rx	Response
12-24 hrs	Replacement of intracellular enzymes
36-48 hrs	BM response (hyperplasia)
48-72 hrs	Reticulocytosis
4-30 days	↑↑ Hemoglobin
1-3 months	Repletion of stores

4. Blood transfusion (*Indicated only in very severe cases*)
  - Rapid hematological response can be achieved by iron therapy
  - Risky procedure: volume overload, HF
  - In severe cases [Packed RBC 2-3 ml/Kg + furosemide] "can be repeated"

## Microcytic Hypochromic Anemias

### Etiology

1. Iron deficiency anemia
2.  $\beta$ -Thalassemia trait: ↑↑ Hb A<sub>2</sub> (3.4-7 %), RDW normal  
Normal iron, TIBC & ferritin
3.  $\beta$ -Thalassemia major: C/P, ↑↑ Hb F, ↑↑ iron & ferritin
4.  $\alpha$ -Thalassemia trait: Diagnosis of exclusion, normal Hb electrophoresis
5. HbH disease ( $\beta_4$ ): mild to moderate hemolytic anemia + splenomegaly + jaundice
6. Anemia of chronic disease
7. Lead poisoning: Basophilic stippling, ↑↑ blood Lead ( $> 10 \mu\text{g/dL}$ ), ↑↑ FEP
8. Atransferrinemia Iron overload, HSM. Iron is deposited in visceral organs rather than BM  
Rx: blood transfusion + chelating agent + apo-transferrin
9. Familial deficient iron absorption (Parenteral iron)
10. Sideroblastic anemia (Sideros = iron)

**Definition:** Inherited or acquired disorders characterized by defective heme synthesis, refractory anemia & ring sideroblast in BM

**Ring sideroblast:** BM nucleated RBC precursors with retention of iron in the mitochondria in the form of perinuclear iron granules (defective heme synthesis)

### Etiology

1. Congenital sideroblastic anemia (XLR)
2. Pearson's syndrome (Macrocytic)
3. Acquired: (Isoniazide, alcohol, Lead, MDS)

### Treatment

1. Pyridoxine (B<sub>6</sub>)
2. Blood transfusion
3. HSCT

# Hemolytic Anemia

## Definition

↓↓ RBC life span due to premature destruction. Hemolysis may be extra or intravascular

## Etiology

- A) **Intracorpuseular (Intrinsic):** Membrane, Enzyme & Hb defects
- B) **Extracorpuseular (Extrinsic):** Immune & non-immune causes

## Pathophysiology (RBC Destruction & Compensatory mechanisms)

### **RBC Destruction**

- Anemia (↓↓ RBC life span)
- ↑↑ Indirect bilirubin (unconjugated)
- ↑↑ Stercobilinoge & urobilinogen
- ↑↑ Serum iron
- RES hyperplasia
- ↓↓ Haptoglobin (in intravascular)

### **Compensatory mechanisms**

- BM erythroid hyperplasia (6-8 folds)
- ↓↓ M/E ratio (N=2-4 : 1)
- Expansion of marrow spaces
- ↑↑ Retics
- ↑↑ blood normoblasts
- HSM (extramedullary hemopoiesis)

## Clinical picture

- A) **Anemia** (Pallor...)
- B) **Hemolytic jaundice** (3 colors):
  - Eye: jaundice
  - Stools: dark
  - Urine: normal (darkens on standing, why?)
- C) **HSM**
  - Destruction of RBCs
  - Hemosiderosis (iron overload due to ↑↑ hemolysis, ↑↑ absorption & blood transfusion)
  - Extramedullary hematopoiesis
  - Anemic HF
  - Viral hepatitis
- D) **Gall stones** (obstructive jaundice)
- E) **Skeletal manifestation** (Mongoloid facies)
 

Large head, prominent maxillae, protruding central incisors, short broad hands
- F) **Manifestations of hemosiderosis**
  - Heart: Cardiomyopathy & arrhythmias
  - Endocrinal: Pituitary (short stature), Gonads (hypogonadism), DM, Thyroid, hypoparathyroidism...
  - Liver cirrhosis
  - Skin pigmentation (skin bronzing- bronze diabetes)
- G) **Different types of crises**
  - a. **Hemolytic crisis** (Aggravation of anemia with deepening of jaundice)
 

C/P: Fever, bony pains, ↑↑ pallor, ↑↑ jaundice

Lab.: ↑↑ Retics
  - b. **Aplastic crisis** (Aggravation of anemia without deepening of jaundice)
 

C/P: ↑↑ pallor, No ↑↑ jaundice

Lab.: ↓↓ Retics

Parvovirus B<sub>19</sub>
  - c. **Sequestration crisis** (Aggravation of anemia with splenomegaly)
 

C/P: ↑↑ pallor, splenomegaly (sudden massive pooling of blood in the spleen)
  - d. **Megaloblastic crisis** (relative folic acid deficiency)
  - e. **Vaso-occlusive crisis** (only in sickle cell anemia)

## Investigations

### A) For diagnosis of hemolytic anemia

- CBC: anemia (normocytic or microcytic)
- Reticulocytosis
- Blood film:
  - Target cells (Hb is concentrated in the center of RBC): Thalassemia, Hb CC
  - Sickle cells: Sickle cell disease & trait (spontaneous in disease, induced in trait)
  - Spherocytes (small, rounded with lack of central pallor): HS, autoimmune HA
  - Elliptocytes (oval cells): in hereditary elliptocytosis
  - Stomatocytes (elongated slit replacing the central pallor): in H. stomatocytosis
  - Acanthocytes (multiple spiny projections): in abetalipoproteinemia
  - Heinz bodies (aggregated denatured Hb): G-6-PD deficiency & unstable Hb
  - Howell-Jolly bodies (small basophilic inclusions): asplenia (congenital, surgical or functional hyposplenism Hb SS)
- BM examination (aspirate/ biopsy): hypercellular with ↓↓ or reversed M/E ratio
- Serum: ↑↑ Indirect bilirubin, ↑↑ Iron
- Stools: ↑↑ Stercobilinogen
- Urine: ↑↑ urobilinogen
- ↓↓ RBC life span: 51-Cr tagged RBCs
- X-rays: widening of diploic spaces & hair-on-end appearance

### B) For differentiation between intra & extravascular hemolysis

- Hemoglobinemia
- Hemoglobinuria
- Hemosiderinuria
- ↓↓ plasma haptoglobin (Haptoglobin combines with free Hb & cleared by RES)
- ↓↓ plasma hemopexin (Hemopexin combines with free heme & cleared by RES)

### C) For diagnosis of the cause

- Blood film
- Osmotic fragility (fresh & incubated)
- Acidified glycerol lysis test "AGLT" (fresh & incubated)
- Hb electrophoresis & HPLC
- Sickling test
- Enzyme assay (G-6-PD)
- Coomb's test
- Ham's test (acidified serum lysis test) & Sucrose lysis test

## Membrane Defects of RBC

### Classification

#### A) Inherited:

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary pyropoikilocytosis
- Hereditary stomatocytosis

#### B) Acquired: PNH, abetalipoproteinemia & vitamin E deficiency

## Enzymatic Defects of RBC

### Classification

#### A) Glycolysis Pyruvate kinase deficiency

Phosphofructokinase deficiency (hemolysis + myopathy GSD VII)

#### B) Hexose Monophosphate shunt (Pentose shunt)

- G-6-PD deficiency
- Glutathione & Glutathione reductase deficiency

## Hereditary Spherocytosis

### Definition

Chronic hemolytic anemia due to hereditary defect of RBC membrane

### Etiology

Autosomal dominant (25% new mutation)

Membrane cytoskeletal protein defects involving spectrin, ankyrin or band 3

- Loss of plasticity (↓↓ deformability)
- ↑↑ Na & water permeability → ↑↑ ATP use & metabolic work

↑↑ Destruction

**Clinical picture** (Onset = *may* present in the neonatal period; NJ & anemia)

- May be asymptomatic: Variation in gene expression "penetrance & expressivity"
- General features of chronic hemolytic anemia

### Investigations

- General investigations of chronic hemolytic anemia
- CBC: normocytic, spherocytes, ↑↑ MCHC
- Osmotic fragility (RBCs are placed in hypotonic saline): "fresh & incubated"  
Normally, hemolysis starts at 0.45% & is complete at 0.35%  
In HS: hemolysis starts at higher concentrations (i.e., more fragile)  
This finding is accentuated by depriving the cells of glucose "incubated test"
- AGLT (fresh & incubated)
- Membrane cytoskeletal protein analysis (electrophoresis)
- DNA analysis

DD: Immune hemolytic anemia

### Treatment

1. Mild cases (Hb > 10 g %): No Rx (just folic acid)
  2. Severe cases (Hb < 10 g %): Packed RBC + folic acid ± splenectomy (better > 5yrs)
- Partial splenectomy can be done in children < 5 yrs  
Laparoscopic splenectomy is safe in children  
Selective angio-embolization of splenic artery branches can be done (postoperative pain)
- Precautions with splenectomy:** (see later)

Post splenectomy sepsis

#### Splenectomy:

1. Clinical cure (anemia & jaundice)
2. Biochemical & morphological abnormalities are not corrected
3. Spherocytes & osmotic fragility ↑↑

## Hereditary Elliptocytosis

## Hereditary Pyropoikilocytosis

## Hereditary Stomatocytosis

	Elliptocytosis	Pyropoikilocytosis	Stomatocytosis
<b>Etiology</b>	Membrane cytoskeletal protein defects		
<b>C/P</b>	General features of chronic hemolytic anemia (as H.spherocytosis)		
<b>Blood film</b>	Elliptocytes (oval)	Microcytosis, Aniso-Poikilocytosis ↑↑ Thermal instability	Stomatocytes (Elongated slit replacing the central pallor)
<b>Rx</b>	Packed RBC + folic acid ± splenectomy		Splenectomy is not recommended (↑↑ thrombosis)

## Paroxysmal Nocturnal Hemoglobinuria

### Definition

Chronic hemolytic anemia due to acquired defect of RBC membrane

### Etiology (Not inherited)

- ↑↑ **Susceptibility** to damage by **complement** system due to defect in cell membrane proteins that normally inhibit membrane protein
- Deficient proteins include decay-accelerating factor & C8 binding protein
- This abnormality affects marrow stem cells (*Dyserythropoietic anemia*), WBC & platelets

### Pathophysiology

- Intravascular hemolysis (hemoglobinuria...)
- Nocturnal hemolysis is classic, but chronic hemolysis is more common
- Sleeping (↓↓ RC) → Mild respiratory acidosis → ↑↑ complement lysis (hemolysis)
- WBC & PLT are also affected → release of thrombogenic substances → thrombosis

### Clinical picture

- General features of chronic hemolytic anemia (jaundice, splenomegaly...)
- Dark urine (hemoglobinuria)
- Thrombosis (abdominal pain, stroke...) & infection
- Complications: Aplastic anemia & AML

### Investigations

- General investigations of chronic hemolytic anemia
- Intravascular hemolysis (*mention*)
- ↓↓ Retic (Dyserythropoietic anemia)
- ↓↓ WBC & PLT
- ↓↓ serum iron (hemosiderinuria)
- Ham's test (acidified serum lysis test) & Sucrose lysis test [↑↑ complement lysis]
- BM examination (aspirate/ biopsy): Aplastic anemia & AML
- Flow cytometry for CD59

### Treatment (No definitive therapy)

- Anemia (folic ± blood transfusion)
- Anticoagulant
- Analgesics for pain
- Iron therapy (*The only hemolytic anemia...*)
- Prednisone & BM transplantation
- Rx of infection, aplastic anemia & AML

## Abetalipoproteinemia (Acanthocytosis)

### Etiology (AR)

- Absent Apo B-48 (Intestine) → No chylomicrons → Fat malabsorption (steatorrhea)
- Absent Apo B-100 (Liver) → No VLDL & No LDL (↓↓ serum cholesterol & triglycerides)

### Clinical picture

- FTT, steatorrhea, rickets
- Neurological (2<sup>nd</sup> decade): ataxia, PN, deep sensory loss & retinitis pigmentosa
- Hematological: acanthocytes (multiple spiny projections)

### Treatment

Medium-chain triglycerides & Vitamin E, A, D, K

Myopathy  
Neuropathy  
Anemia

## Vitamin E Deficiency (tocopherol)

- Vitamin E is **antioxidant**. It prevents peroxidation of RBC membrane lipids (PUFA)
- Deficiency occurs in\* preterm & steatorrhea. Oxidants (e.g., iron) will lead to hemolysis
- *Prophylactic* = 0.5-1.5 mg/d *Therapeutic* = 5-30 mg/d [↑↑ PUFA → ↑↑ Vit.E requirements]

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Chronic hemolytic anemia due to acquired defect of RBC membrane

### Etiology (Not inherited)

- ↑↑ **Susceptibility** to damage by **complement** system due to defect in cell membrane proteins that normally inhibit membrane protein
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- General investigations of chronic hemolytic anemia
- Intravascular hemolysis (*mention*)
- ↓↓ Retics-(Dyserythropoietic anemia)
- ↓↓ WBC & PLT
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Medium-chain triglycerides & Vitamin E, A, D, K

Myopathy Neuropathy Anemia
----------------------------------

## Vitamin E Deficiency (tocopherol)

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- Deficiency occurs in\* preterm & steatorrhea. Oxidants (e.g., iron) will lead to hemolysis
- *Prophylactic* = 0.5-1.5 mg/d *Therapeutic* = 5-30 mg/d [↑↑ PUFA → ↑↑ Vit.E requirements]

## Pyruvate Kinase Deficiency

### Etiology (AR)

↓↓ Pyruvate kinase enzyme → ↓↓ ATP production → ↓↓ RBC life span

### Clinical picture (Onset = *may* present in the neonatal period; NJ & anemia)

- May be asymptomatic (adulthood)
- General features of CHA (mild pallor & splenomegaly)

### Investigations

- General investigations of chronic hemolytic anemia
- ↓↓ Pyruvate kinase enzyme

### Treatment

1. Management of NJ
2. Packed RBC
3. Splenectomy (better > 5 yrs)

## Glucose-6-Phosphate Dehydrogenase Deficiency

### Etiology (XLR)

HMP shunt defect → ↓↓ G-6-PD enzyme → ↓↓ NADPH production → ↓↓ Reduced glutathione →  
 ↓↓ Reduction of  $H_2O_2$  → Hb oxidation, denaturation & precipitation → Heinz bodies →  
 ↑↑ RBC destruction

### Physiology

There are > 100 enzyme variants of G6PD

G-6-PD B <sup>+</sup> is the normal enzyme	] Polymorphism
G-6-PD A <sup>+</sup> is a normal variant	
G-6-PD B <sup>-</sup> (5-40 % activity)	] Abnormal variants.
G-6-PD A <sup>-</sup> (5-15 % activity)	

Hemolysis occurs in patients with G6PD deficiency on exposure to certain drugs (oxidant stress)

### Precipitating Factors

1. Fava beans (Mediterranean type; *favism*)
2. Drugs: **Antibiotics** (Sulfa, chloramphenicol, nitrofurantoin)  
**Antimalarial** (chloroquine, primaquine), **others** (aspirin, Vit K, methylene blue)
3. Chemicals: benzene & naphthalene
4. Infection: hepatitis & DKA
5. Idiopathic

### Clinical picture (Onset = *may* present in the neonatal period; NJ & anemia)

Acute hemolytic crisis: History of exposure... (24-48 hours)

Sudden onset of Pallor, Jaundice (Indirect), Dark urine (Hb)

**NB:** Chronic hemolytic anemia is a rare presentation of G-6-PD deficiency

### Investigations

- Investigation of hemolytic anemia + intravascular hemolysis (*mention*)
- ↓↓ G-6-PD enzyme activity (done 3 weeks after the onset of hemolysis, why??)
- Neonatal screening may be done (Mediterranean)

### Treatment

1. Management of NJ
2. Prevention [Avoid...]
3. Packed RBC

#### DD of Acute hemolytic anemias:

1. G6PD & PK deficiency
2. Hemolytic crisis of CHA
3. AIHA
4. HUS
5. Infection
6. Metabolic (porphyria & Wilson)

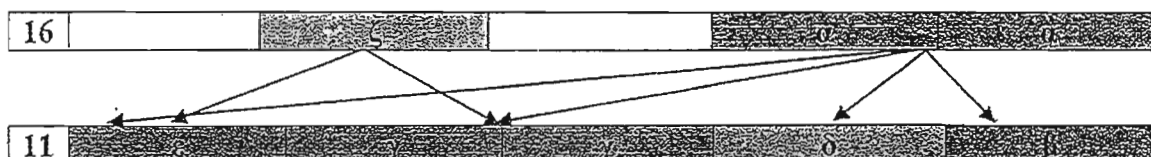
# Hemoglobin Disorders

Hb is tetramer

There are &gt; 800 Hb variants

## Physiology

- Hemoglobin is formed of:
  - Heme (= iron  $\text{Fe}^{++}$  protoporphyrin): Not genetically determined
  - Globin: 4 polypeptide chains ( $2\alpha + 2\text{non } \alpha$ ); each chain contains a heme group
- Globin part is genetically determined. Two families of genes are responsible:
  - $\alpha$  Gene family ( $2\alpha$  genes & 1  $\zeta$  gene)  $\rightarrow$  141 aa
  - $\beta$  Gene family ( $\beta$  gene,  $\delta$  gene, 2  $\gamma$  genes &  $\epsilon$  gene)  $\rightarrow$  146 aa



## Normal Hemoglobin

Normal Hb	Name	Structure
Embryonic Hb	Gower I	$2\zeta + 2\epsilon$
	Gower II	$2\alpha + 2\epsilon$
	Portland	$2\zeta + 2\gamma$
Fetal Hb	Hb F	$2\alpha + 2\gamma$
Adult Hb	HbA	$2\alpha + 2\beta$
	HbA <sub>2</sub>	$2\alpha + 2\delta$

- Zeta ( $\zeta$ ) & Epsilon ( $\epsilon$ ) genes stop working by the 3<sup>rd</sup> month of pregnancy
- By the 3<sup>rd</sup> month of pregnancy, Hb F is the major Hb

	At Birth	6-12 months
Hb A	20-30 %	97-98 %
Hb F	70-80 %	0-2 %
Hb A <sub>2</sub>	-	2-3.4 %

### Diagnosis of Hb disorder:

- Hb electrophoresis
- High performance liquid chromatography (HPLC)

Hb disorders affecting  $\beta$ -chains manifest after 6 months. Why??

## Abnormal Hemoglobin

Abnormal Hb	Structure
Hb S	$2\alpha + 2\beta^{\text{valine}}$
Hb C	$2\alpha + 2\beta^{\text{lysine}}$
Hb D	Variable
Hb E	$2\alpha + 2\beta^{26\text{ lysine}}$
Hb H	$4\beta$
Hb Barts	$4\gamma$
Hb M	$\uparrow\uparrow$ tendency to oxidation ( $\uparrow\uparrow$ Met Hb formation)
Hb Lepore	Fusion of $\beta$ & $\delta$ genes
Hb constant spring	$\uparrow\uparrow$ $\alpha$ chain by extra 31 aa (sense mutation)

- During fetal life & early childhood, HbF & HbA ( $\beta$  &  $\gamma$ ) are inversely proportionate
- 3 months before birth,  $\downarrow\downarrow \gamma$  &  $\uparrow\uparrow \beta$  synthesis (Hb switch)

### $\uparrow\uparrow$ HbF:

1. Thalassemia (major & trait)
2. HPFH
3. B chain hemoglobinopathy (sickle...)
4. Hematologic stress: aplastic anemia, HA, Diamond-Blackfan  $\delta$ , leukemia
5. r-HuEPO therapy

## Classification of Hb Disorders

A) Qualitative (Hemoglobinopathy) [Structural defects] Hb S, Hb C, Hb M...

- a. Sickle cell disease & sickle cell trait
- b. HbC, HbD, HbE
- c. Unstable Hb

B) Quantitative [ $\downarrow\downarrow$  formation of  $\alpha$  or  $\beta$  chains]

- a.  $\beta$  Thalassemia [ $\downarrow\downarrow$  formation of  $\beta$  chains]
- b.  $\alpha$  Thalassemia [ $\downarrow\downarrow$  formation of  $\alpha$  chains]
- c. Hereditary persistence of fetal Hb (HPFH): failure of switch from  $\gamma$  to  $\beta$  chain



# Sickle Cell Anemia

## (Homozygous Hb SS)

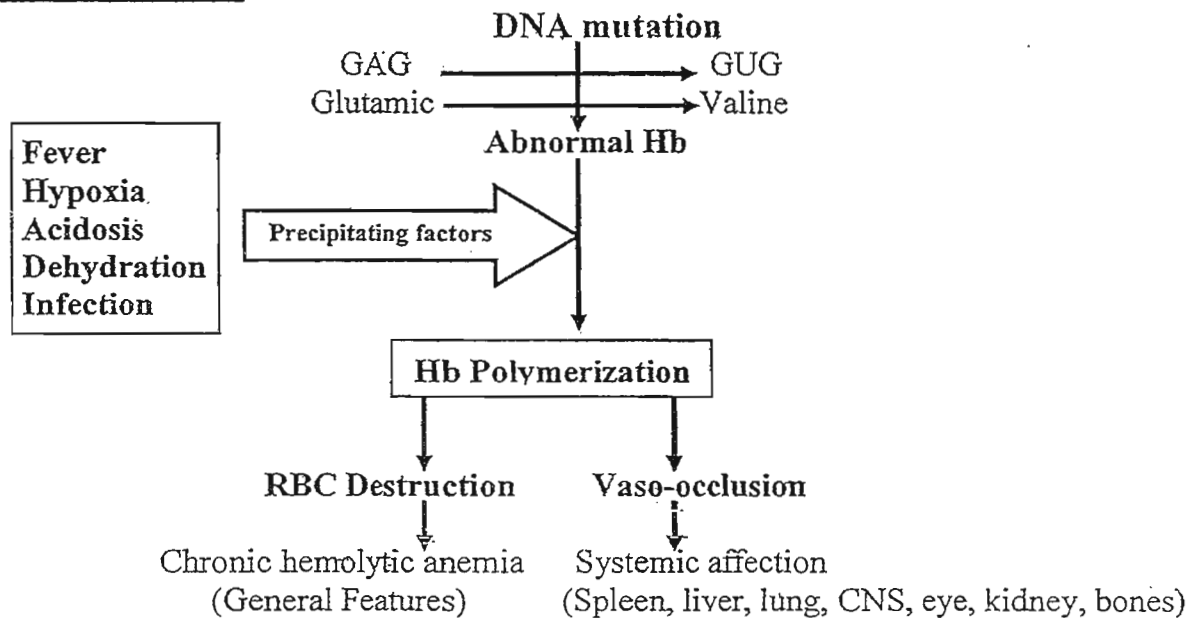
### Definition

It is chronic hemolytic anemia due to homozygous occurrence of sickle gene

### Etiology & Genetics (Incomplete AD)

- Point mutation in **both**  $\beta$ -genes (i.e., **homozygous**)
- Abnormal structure of  $\beta$ -chains (valine replaces glutamic acid the 6<sup>th</sup> aa from amino end)
- Both parents are carriers (sickle cell trait)
- Hb-electrophoresis = No HbA, HbS 80-95%, HbF 2-20%

### Pathophysiology



### Clinical picture (Onset = 2<sup>nd</sup> half of the 1<sup>st</sup> year)

1. General features of CHA (No splenomegaly)
  2. Vaso-occlusive crisis
  3. Sequestration crisis
  4. Aplastic crisis
  5. Hyperhemolytic crisis (G6PD deficiency is a possible cause)
  6. Organ dysfunction
    - ☑ Liver: hepatomegaly, Gall stones, transfusion-related hepatitis & cirrhosis
    - ☑ Eye: retinopathy, blindness
    - ☑ Skin: leg ulcers
    - ☑ Kidney:
      - Hypothenuria (urine concentration defect due to affection of vasa recta)
      - Acquired nephrogenic DI & RTA (due to interstitial fibrosis)
      - Hematuria (due to papillary necrosis) Rx: Aggressive IV hydration
      - Proteinuria & nephrotic S: Rx: ACE inhibitors (captopril)
      - CRF (due to chronic interstitial nephritis & focal scarring)
    - ☑ Cardiomyopathy: (due to anemia, VOC & hemosiderosis)
    - ☑ Lung: ACS, pulmonary fibrosis, pulmonary hypertension & cor-pulmonale
    - ☑ Spleen (functional hyposplenism): ↑↑ risk of infection 300 folds (Max. in 1<sup>st</sup> 5yrs)
- Organisms: Pneumococci, Haemophilus influenza, Meningococci & Salmonella
- ☑ CNS: neuropsychological deficit (IQ, speech, seizures & motor deficits)

**Autosplenectomy**

Stroke may be:  
1. Overt (C/P)  
2. Silent (MRI)

## Clinical picture of vaso-occlusive crisis

1. Hand-foot syndrome (Acute sickle dactylitis): Painful swelling usually < 5 yrs
2. Bone crisis: Fever, pain, tenderness & swelling usually affecting multiple sites  
[↓↓ Uptake by *bone scan*. DD: Osteomyelitis]
3. Abdominal crisis: due to affection of mesenteric vessels [DD: Acute abdomen]
4. Intra-hepatic crisis (Hepatic sequestration): Sudden painful liver enlargement with ↑↑ bilirubin & liver enzymes [DD: Acute hepatitis]
5. Acute chest syndrome (ACS): Chest pain, dyspnea & fever [normal CXR & abnormal V/Q scan. DD: Pneumonia]
6. CNS crisis: Convulsions, motor deficits, meningeal signs, stroke & blindness
7. Hematuria: mild & painless (due to papillary necrosis)
8. Priapism (due to papillary necrosis)

## Investigations

- General investigations of chronic hemolytic anemia
- CBC: Normocytic normochromic anemia (mid to moderate), sickle cells & Howell-Jolly bodies, ↑↑ WBC, ↑↑ PNL, ↑↑ Retic
- ↓↓ ESR (sickling)
- Sickling test: Induction of sickling of RBC by deoxygenation or addition of reducing substances (Na metabisulphite)
- Hb electrophoresis & HPLC: No HbA, HbS 80-95%, HbF 2-20%
- Transcranial Doppler (TCD): ↑↑ blood flow velocity in the cerebral arteries (> 200cm/sec) is associated with ↑↑ risk of stroke & is an indication of chronic transfusion therapy to maintain HbS < 30 %. TCD is done yearly starting at the age of 2-3 years
- Investigations of organ dysfunction: bone scan, lung scan, echo-, KFTs, LFTs...
- Neonatal screening & antenatal diagnosis (using restriction enzymes e.g., Mst II...)

## Treatment

1. Parent education (temperature, palpation of spleen, symptoms of sickle cell disease)
2. Folic acid
3. Vaccination: HBV, Hib, meningococcal vaccines  
PCV (pneumococcal conjugate v): 2, 4, 6 & 15 months (routine in USA)  
PPV (pneumococcal polysaccharide v): at 2 yrs of age
4. Penicillin prophylaxis starting at the age of 2 months;  
Children < 3 yrs 125 mg twice daily  
Children > 3 yrs 250 mg twice daily  
Allergic patients → Erythromycin } Continue till the age of 5 yrs
5. Patients with fever  
- Thorough examination  
- Investigations: (CBC, CXR, blood & urine cultures)  
- All patients < 5 yrs with documented fever should be admitted  
- Ceftriaxone (75 mg/Kg/d) is the drug of choice
6. Aplastic & hyperhemolytic crisis: Blood transfusion
7. Sequestration crisis:  
- Blood transfusion ± exchange transfusion  
- Splenectomy in recurrent/ severe cases
8. Acute chest S (ACS):  
- Oxygenation & Respiratory support  
- Blood transfusion (Do Not ↑↑ Hb > 11 g %)  
- Exchange transfusion (if hypoxemia, marked RD or Rt sided HF) to ↓↓ HbS < 30%  
- Pain control  
- Antibiotics (e.g., Ceftriaxone)

## 9. Management of neurological complications (stroke)

- Oxygenation
- Blood transfusion (Do Not  $\uparrow\uparrow$  Hb  $> 11$  g %)
- Exchange transfusion ( $\downarrow\downarrow$  HbS  $< 30\%$ )
- Secondary prevention: chronic transfusion therapy

## 10. Drug therapy (Hydroxyurea):

Mechanism:  $\uparrow\uparrow$  HbF formation

Side effects: myelosuppression, renal impairment, hair loss & GIT disturbances

Monitoring: monthly CBC, MCV, LFTs, HbF

## 11. Bone marrow transplantation (from HLA matched sibling)

## Treatment of vaso-occlusive crisis

### 1. Hydration (1.5 times maintenance)

### 2. Analgesia

- Paracetamol (15 mg/Kg/dose)
- Aspirin (15 mg/Kg/dose)
- Ibuprofen (15 mg/Kg/dose)
- Morphine (0.15 mg/Kg/dose) IM
- Meperidine (1.5 mg/Kg/dose) IM
- Codeine (0.75 mg/Kg/dose) PO

### 3. Blood transfusion/ exchange transfusion

#### Indications of blood transfusion/ exchange transfusion:

1. Anemia
2. Refractory painful crisis
3. Splenic sequestration
4. Stroke
5. Acute chest S
6. Elective surgery (anesthesia)
7. Priapism
8. Pregnancy (latter part)

#### Aim:

To  $\downarrow\downarrow$  HbS  $< 30\%$

#### Hemoglobin S- $\beta$ Thalassemia:

##### Genetics:

The presence of genes for HbS & thalassemia

1. HbS-B<sup>+</sup>: HbS (60-80%) + HbA (<30%) + mild  $\uparrow\uparrow$  HbF & HbA<sub>2</sub>
2. HbS-B<sup>0</sup>: HbS + No-HbA (exactly as-SS)

	HbSS	HbS-B <sup>0</sup>
MCV	Normocytic	Microcytic
Parents	Both are sickle cell trait	HbAS Thalassem. trait

C/P: Variable

VOC + splenomegaly

#### Sickle cell syndromes:

Sickle cell anemia (SS)	S- $\beta^0$ Thalassemia
Sickle cell trait (AS)	S- $\beta^+$ Thalassemia
Hemoglobin SC	S-HPFH

#### Sickle cell disease:

Sickle cell anemia (SS)  
Compound heterozygous e.g,  
S- $\beta^+$ Thalassemia, Hb SC, S-HPFH

## Sickle Cell Trait

(Hb AS)

### Genetics

Heterozygous mutation of  $\beta$  gene (valine replaces glutamic acid...)

Hb electrophoresis: HbA 60 % + HbS 40 % (AS pattern)

### Clinical picture

- Asymptomatic under normal conditions
- Sudden death may occur during vigorous exercises
- VOC can occur with hypoxemia (shock, flying, high altitudes & GA)
- Genetic counseling (when both parents are trait, there is 25% risk of sickle cell anemia)

Treatment No restriction of activities

# Thalassemia Syndromes



## Definition

Chronic hemolytic anemia due to inherited quantitative defect of Hb caused by:

- Deficient synthesis of one of the globin chains ( $\alpha$  or  $\beta$  chains)
- The **imbalanced** chain production leads to **precipitation** of globin chains in:
  - Bone marrow RBC precursors: Dyserythropoietic anemia
  - Circulating RBCs: Hemolytic anemia (Intra-corpuscular- extravascular)

## Classification & Genetics

### A) $\beta$ Thalassemia [ $\downarrow\downarrow$ formation of $\beta$ chains]

$\beta^0$  = absent  $\beta$ -chain synthesis       $\beta^+$  = reduced  $\beta$ -chain synthesis

#### Genetics:

- Point mutation:** affecting transcription, mRNA splicing or translation
- Deletion:** of  $\beta$  gene
- Hb Lepore:** fusion between  $\beta$  and  $\delta$  genes (unequal crossing-over)

### B) $\alpha$ Thalassemia [ $\downarrow\downarrow$ formation of $\alpha$ chains]

#### Genetics:

- Deletion:** of  $\geq$  one of the 4  $\alpha$  genes (silent carrier, trait, HbH, hydrops fetalis)
- Chain terminator defect:** sense mutation of stop codon leading to  $\alpha$  chain with an extra 31 aa (Hb Constant Spring)

### C) Hereditary persistence of fetal Hb (HPFH): failure of switch from $\gamma$ to $\beta$ chain

## $\alpha$ -Thalassemias

### Definition

Deficient synthesis of  $\alpha$ -chain due to ~~deletion~~ or mutation of  $\alpha$  gene (Hb Constant Spring)  
Hemolysis is caused by precipitation of free  $\beta$  &  $\gamma$  chains

### Classification

According to the number of deleted genes:

Syndrome	# Gene	Genotype	Hematological	C/P	Hb
$\alpha$ -Silent carrier	1	- $\alpha$ / $\alpha\alpha$	Normal	Normal	Neonate: Hb Barts (1-2 %)
$\alpha$ -Thalassemia trait	2	- $\alpha$ / - $\alpha$ or - / $\alpha\alpha$	Microcytosis Hypochromia	Normal Mild anemia	Neonate: Hb Barts (5-10 %)
HbH disease	3	- $\alpha$ / - -		Mild H. anemia	Neonate: Hb Barts (20-30 %)
Hydrops fetalis	4	- - / - -	Anisocytosis Poikilocytosis	Death IU or Early neonatal	Neonate: Hb Barts (80-90 %)

HbH disease: mild to moderate hemolytic anemia + splenomegaly + jaundice + Transfusion is usually not required. Hydrops fetalis: transfusion + BM transplantation (the only cure)

## Hereditary Persistence of Fetal Hb

### Definition

Failure of switch from  $\gamma$  to  $\beta$  chain commonly caused by deletion of  $\beta$  and  $\delta$  genes

### Clinical Picture

Homozygous: mild anemia + microcytosis + HbF (100 %)

Heterozygous: HbF (20-40 %)

Sickle-HPFH: **mild** manifestation (HbF prevents sickling)

## $\beta$ -Thalassemia Syndromes

### Definition

Deficient synthesis of  $\beta$  chain due to mutation or deletion of  $\beta$  gene. It may be  $\beta^0$  or  $\beta^+$   
Hemolysis is caused by precipitation of free  $\alpha$ -chain.

### Classification

1. **Homozygous  $\beta$  Thalassemia** [Thalassemia major;  $\beta^0\beta^0$  or  $\beta^+\beta^+$ ]
2. **Heterozygous  $\beta$  Thalassemia** [Thalassemia trait;  $\beta^0\beta^0$  or  $\beta^+\beta^+$ ]
3. **Special phenotypic type** [Thalassemia Intermedia]

Concomitant $\alpha$ -thalassemia ameliorates the C/P of $\beta$ -thalassemia
---

## Thalassemia Trait (Thalassemia minor)

### Genetics

Heterozygous  $\beta^0$  or  $\beta^+$

### Clinical picture

Asymptomatic (normal examination). Discovered accidentally

### Investigations

Mild microcytic hypochromic anemia (RDW normal or  $\uparrow\uparrow$ )

Normal iron, TIBC & ferritin

$\uparrow\uparrow$  Hb A<sub>2</sub> (3.4-7 %) & mild  $\uparrow\uparrow$  Hb F (2-6 %)

### Importance

- DD of iron deficiency anemia
- Genetic counseling (when both parents are trait, there is 25% risk of thalassemia major)

## Thalassemia Major (Cooley's anemia)

### Genetics

Homozygous  $\beta^0$  or  $\beta^+$

**Clinical picture** (Onset = 2<sup>nd</sup> half of the 1<sup>st</sup> year)

General features of CHA (*mention*)

Hb A is <i>absent</i> in $\beta^0$ thalassemia & <i>decreased</i> in $\beta^+$ thalassemia
--

### Investigations

- General investigations of chronic hemolytic anemia (Hb < 5 g %)
- Assessment of iron overload: serum ferritin, specialized MRI, liver biopsy
- Hb electrophoresis & HPLC: HbF > 70 %, normal Hb A<sub>2</sub> and Hb A is *absent* or *decreased*

## Thalassemia Intermedia

### Genetics

Homozygous  $\beta^0$  or  $\beta^+$  (?? modified by associated  $\alpha$ -thalassemia or HPFH)

**Clinical picture** (General features of thalassemia), but...

- Onset: after 2 years of age
- Hb level: maintained between 6-8 g %
- Do not require regular blood transfusion
- Extramedullary hematopoiesis can occur in the vertebral canal (neurologic symptoms)

**Investigations** General investigations of chronic hemolytic anemia

### Treatment

1. Transfusion: Controversial
2. Local radiation therapy for vertebral canal hematopoiesis ( $\downarrow\downarrow$  erythropoiesis)
3. Splenectomy may be needed
4. L-carnitine & Hydroxy urea

## Treatment of Thalassemia (& CHA)

### A) Blood transfusion

**Target:** Post transfusion Hb = 9.5 g%

Hypertransfusion (Hb > 10g %) & supertransfusion (Hb > 12g %) should be avoided, why?

**Value:**

- Improve activity & growth
- Improve cardiac function
- # BM expansion (cosmetic)
- ↓↓ GIT iron absorption

**Amount:** 10-20 ml/ Kg every 4-5 weeks

**Type of blood:**

- Fresh (? Neocyte)
- CMV free
- Phenotypically matched (including minor blood groups; kell...)
- Filtered (Leukocyte depleted)
- Irradiated (if BM transplantation)
- Washed (↓↓ plasma proteins)
- ?? Paired donor & recipient

RBC phenotype should be obtained at diagnosis

**Neocyte transfusion:** young RBC with ↑↑ life span → ↓↓ frequency of blood transfusion

**Paired donor & recipient programs:** are used in some centers (↓↓ Risk of sensitization)

**Causes of ↑↑ Frequency of transfusion:**

- Hypersplenism
- isoimmunization
- Folic acid deficiency

**Complications (mention)**

### B) Iron chelating therapy

**Indications:** when serum ferritin > 1000 ng/ml, usually > 4-5 years

#### I. Deferoxamine (Desferal)

**Dose:** 40-60 mg/Kg/day using portable electronic SC pump over 10-12 hrs/day for 5-6 days/week. IV Deferoxamine may be used in severe cases

**Side effects:**

- Ototoxicity
- ↓↓ Visual field & acuity
- Local: pruritis, swelling & rash.

#### 2. Deferiprone (L-1): Oral chelating agent

**Side effects:** Neutropenia

#### 3. ICL 670: Oral chelating agent

### C) Splenectomy

**Indications:**

- Massive splenomegaly
- ↑↑ Frequency of transfusion (hypersplenism): > 240 ml/Kg/year

**Vaccination:** Before splenectomy (Hib, meningococcal & pneumococcal vaccines)

**Penicillin prophylaxis:** After splenectomy

**Methods:**

- Total splenectomy
- Partial splenectomy
- Laparoscopic splenectomy
- Angio-embolization

#### **Causes of osteoporosis:**

- BM expansion (pressure)
- Deficiency of sex hormones
- Nutritional deficiency

### D) Folic acid & Vitamin D & Calcium

### E) Vaccination

F) Diet Avoid iron rich food + "cup of tea" with each meal to ↓↓ iron absorption

G) Rx of osteoporosis sex hormone replacement (adolescence), calcitonin & bisphosphonate

H) BM Transplantation from HLA matched sibling, successful specially in children < 15 yrs without hepatomegaly, iron overload and with previous few transfusions

I) Hydroxyurea: ↑↑ HbF

J) Gene therapy: activation of γ gene → ↑↑ HbF

# Complications of Blood Transfusion

## Acute Transfusion Reactions

### Acute hemolytic reaction

- ☒ **Cause:** Incompatible blood transfusion "Clerical error"
- ☒ **Clinical Picture:** Fever, chest pain, back pain, RD, tachycardia, hypotension, DIC
- ☒ **Prevention:** Proper cross-matching
- ☒ **Treatment:**
  - DC transfusion
  - IV fluids: Normal saline or lactated Ringer's + Urine alkalinisation
  - Diuretics (furosemide)
  - Dopamine (renal dose?)
  - Dialysis

**Filtered blood:** leukocyte depleted

### Febrile non-hemolytic transfusion reaction

- ☒ **Cause:** Alloimmunization to antigens on WBCs & platelets (release of cytokines)
- ☒ **Clinical Picture:** Fever + chills (in multi-transfused patients)
- ☒ **Prevention:** Use of filtered blood [± Premedication with antipyretics & hydrocortisone]
- ☒ **Treatment:**
  - DC transfusion (DD: hemolytic reaction)
  - Antipyretics & hydrocortisone

### Allergic reaction

- ☒ **Cause:** Reaction to donor's plasma proteins
- ☒ **Clinical Picture:** Erythema, urticaria, laryngospasm, hypotension, anaphylaxis
- ☒ **Prevention:** Use of washed blood
- ☒ **Treatment:**
  - Mild cases: antihistaminics (Diphenhydramine) & continue blood transfusion
  - Anaphylaxis: Adrenaline & steroids (hydrocortisone)

### Bacterial contamination

- ☒ **Cause:** Bacterial contamination
- ☒ **Clinical Picture:** Fever, hypotension, shock, DIC, sepsis
- ☒ **Prevention:** Proper sterilization & avoid room temperature storage
- ☒ **Treatment:** Broad spectrum antibiotics

## Other adverse effects of blood transfusion

### Delayed hemolytic reaction

### Isosensitization to RBC, WBC or platelet antigens

### Bleeding tendency (↓↓ Platelet & ↓↓ Coagulation factors)

### Graft versus host disease

### Disease transmission

- Viral: HBV, HCV, HIV, CMV, EBV
- Bacterial: Syphilis, bacterial sepsis
- Protozoa: toxoplasmosis, malaria

### Volume overload: HF

### Hypothermia: Massive blood transfusion

### Hypocalcemia: Citrate toxicity

### Hyperkalemia: Old blood

### Iron overload (hemosiderosis)

## blood Products

whole blood, packed RBC, FFP, cryoprecipitate, platelets, granulocytes, coagulation factors, Ig, albumin

# Iron Overload Disorders

## (Hemochromatosis)

### Definition

Excessive deposition of hemosiderin in the tissues;

- RES: hemosiderosis (tissue damage is less serious)
- Parenchymal cells: hemochromatosis

### Classification

Primary (Hereditary)	Secondary (Acquired) "C.H.A."
Hereditary hemochromatosis (adult)	Iron overload occurs due to: <ul style="list-style-type: none"> <li>▪ ↑↑ Hemolysis</li> <li>▪ Blood transfusion</li> <li>▪ ↑↑ GIT iron absorption</li> </ul>
Juvenile hemochromatosis	
Neonatal Iron Storage Disease (NISD)	
Atransferrinemia	

#### A) Hereditary hemochromatosis (HH)

*Etiology:* AR

*Pathogenesis:* ↑↑ GIT iron absorption (up to 20-40 %)

*C/P:* Age = 40-60 years

Liver cirrhosis, skin pigmentation (bronzing) & DM

*Investigation:* ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

*Rx:* ↓↓ dietary iron

Repeated venesection

#### B) Juvenile hemochromatosis

*Etiology:* Not genetic

*Pathogenesis:* Iron deposition mainly in heart & pancreas

*C/P:* Cardiomyopathy, arrhythmias & DM

*Investigation:* ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

*Rx:* ↓↓ dietary iron

Repeated venesection

#### C) Neonatal Iron storage Disease (NISD)

*Etiology:* AR

*Pathogenesis:* Iron deposition in liver, heart & pancreas

*C/P:* Age = 1<sup>st</sup> week of life (usually preterm or SGA)

Hepatomegaly, cholestasis & cirrhosis

*Investigation:* ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

↓↓ albumin, ↓↓ prothrombin concentration, ↓↓ glucose

MRI

Liver biopsy: cirrhosis with ↑↑ hemosiderin

Buccal biopsy: ↑↑ hemosiderin

*Rx:* Anti-oxidants + iron chelating agents

Liver transplantation

*Prognosis:* fulminant liver disease

#### D) Atransferrinemia

Iron overload, HSM. Iron is deposited in visceral organs rather than BM

Microcytic hypochromic anemia

*Rx:* blood transfusion + chelating agent + apo-transferrin



## Extracorpuscular Hemolytic Anemia

### Definition

↓↓ RBC life span due to premature destruction caused by extra-corpuscular factors

### Classification

#### 1. Immune hemolytic anemia

a. **Active:** Autoimmune hemolytic anemia (auto-Ab are formed by the patient)

b. **Passively acquired antibodies:** Isoimmune hemolytic anemia

Hemolytic disease of the newborn (Rh,ABO,minor) & mismatched blood transfusion

#### 2. Nonimmune hemolytic anemia: MAHA, infections, hypersplenism, Wilson, chemicals

## Autoimmune Hemolytic Anemia

### Definition

↓↓ RBC life span due to premature destruction by auto-Ab formed by the patient

### Classification& Clinical Picture

AIH due to warm antibodies	AIH due to cold antibodies
<b><u>Etiology</u></b> <b>1. Primary (Idiopathic)*</b> <b>2. Secondary:</b> Collagen-vascular diseases(SLE,U.colitis) Malignancy (lymphoma) Infections (CMV) <b>3. Drugs (3 mechanisms)</b> Hapten (penicillin) Ternary complex (quinine) Induction of auto-Ab (α-methyldopa)	<b>1. Primary (Idiopathic)</b> (= Primary cold agglutinin disease) <b>2. Secondary</b> (= Secondary cold agglutinin disease) Malignancy (lymphoproliferative) Infections (mycoplasma, EBV) <b>3. Paroxysmal cold hemoglobinuria</b> Due to the presence of cold IgG (not IgM) • Primary • Secondary (viral infection & syphilis)
<b><u>Autoantibodies</u></b> • IgG (monomer) • Active between 35-40° C • Do not require complement for activity • Do not cause agglutination in vitro	• IgM (pentamer) • Active < 37° C (best at 0- 4° C) • Require complement for activity • Cause agglutination in vitro
<b><u>Clinical picture</u></b> <b>A) Acute AIHA:</b> Age= 2-12 years Acute onset of pallor, jaundice & Hb-uria Marked splenomegaly Good response to steroid Full recovery within 3-6 months <b>B) Chronic AIHA:</b> Age >12 years Gradual onset of pallor, jaundice Mild splenomegaly Variable response to steroid Underlying cause is usually present	<b>A) Cold agglutinin disease (1ry&amp;2ry)</b> Hemolysis & Hb-uria follow cold exposure Splenomegaly <b>Rx:</b> Avoid cold + Rx of the cause Immunosuppression& plasmapheresis Rituximab (monoclonal Ab) Poor response to steroid <b>B) Paroxysmal cold hemoglobinuria</b> Age >12 years Gradual onset of pallor, jaundice Mild splenomegaly

## Investigations

- General investigations of chronic hemolytic anemia
- CBC: Normocytic normochromic anemia with ↑↑ Retics (reticulocytosis)
- ↓↓ Platelet in secondary cases (SLE) & Evans \$ (AIHA & thrombocytopenia)
- BM examination (aspirate/ biopsy): hypercellular with ↓↓ or reversed M/E ratio
- Serum: ↑↑ Indirect bilirubin, ↑↑ iron
- Stools: ↑↑ Stercobilinogen
- Urine: ↑↑ Urobilinogen
- ↓↓ RBC life span: <sup>51</sup>Cr tagged RBCs
- Coombs test (for detection of auto-Ab): Most important
  - a. *Direct*: detects Antibodies coating RBCs [at least 250-500 Ab should be present/cell]
  - b. *Indirect*: detects Antibodies circulating in the patient's serum

## Treatment

1. Rx of the cause, avoid drugs... and avoid cold...
2. Blood transfusion
  - Transient benefit: Do not give unless indicated (severe anemia, anemic HF)
  - Difficult to get compatible blood: give *the least incompatible* blood
  - Warming of blood: in AIHA due to cold reacting Ab
3. Steroids: IV methylprednisolone (Solu-medrol) 10-30 mg/Kg/day in acute cases  
Oral prednisone 2 mg/Kg/day (till recovery with gradual tapering)
4. IVIG: block splenic Fc receptors
5. Plasmapheresis: removal of auto-Ab
6. Immunosuppressive
7. Rituximab (anti-CD20): inhibits B-lymphocytes → plasma cells → Ab

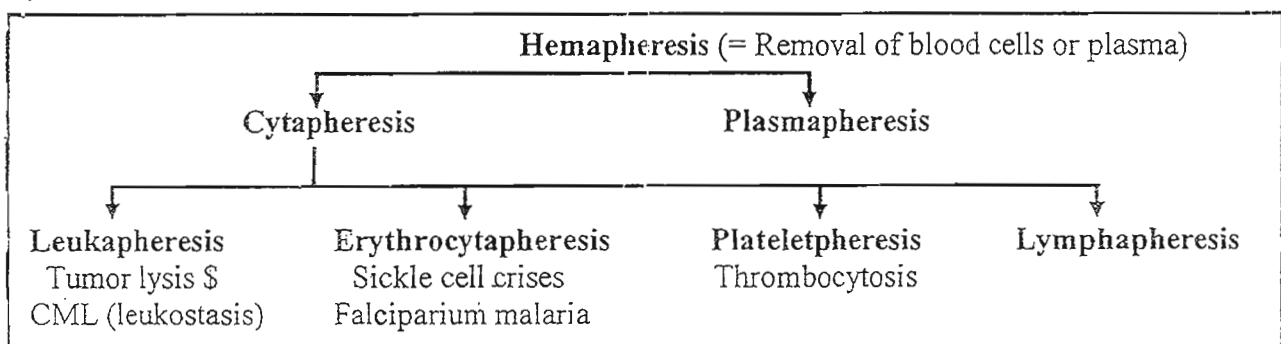
### Indications of plasmapheresis:

1. Autoimmune hemolytic anemia
2. Acute ITP
3. Incompatible blood transfusion
4. Guillain-Barre syndrome
5. Myasthenia gravis
6. HUS
7. TTP
8. RPGN
9. SLE (Lupus nephritis)
10. Goodpasture disease
11. Hyperlipidemia
12. Maternal Ab mediated diseases (Rh...)
13. Intoxication

Replacement fluid: Albumin 5%, FFP or NS

### Indications of exchange transfusion:

1. Sickle cell anemia. When?
2. Cyanotic CHD
3. Polycythemia
4. Hemolytic disease of the NB
5. Neonatal sepsis
6. DIC
7. Neonatal RD (maternal drugs or GA)
8. Hypermagnesemia
9. Inborn errors of metabolism



# Pancytopenia

## Definition

↓↓ of the 3 blood cells RBC, WBC & platelets

## Etiology

### A) Aplastic anemia

#### a. Constitutional: [= Inherited BM failure syndromes]

Fanconi anemia

Dyskeratosis congenita,

Shwachmann-Diamond\$

Amegakaryocytic thrombocytopenia

#### b. Acquired

### B) BM infiltration

- Malignancy: Leukemia
- Osteopetrosis
- Myelofibrosis

### C) Megaloblastic anemia

#### D) ↑↑ Peripheral destruction: Hypersplenism, PNH & Immune (SLE)

## Clinical picture

- Anemia: Pallor
- Thrombocytopenia: Bleeding
- Leucopenia: Infection (fever)

# Constitutional Aplastic Anemia

## Definition

↓↓ of the 3 blood cells RBC, WBC & platelets due to an inherited etiology

### A) Fanconi anemia\*\* (AR)

- Short stature
- Microcephaly, Microphthalmia
- Skin pigmentation (café-au-lait patches)
- Mental retardation & hyperreflexia
- Thumb anomalies (triphalangeal or hypoplastic)
- Radius anomalies
- Renal anomalies (ectopic, dysplasia or horseshoe)
- Pancytopenia (mean age = 6-8 yrs)
- ↑↑ risk of malignancy (leukemia)

#### DD of café-au-lait spots:

1. Neurofibromatosis
2. Fanconi anemia
3. McCune Albright \$
4. Chediak-Higashi \$
5. Ataxia telangiectasia
6. Bloom \$
7. Tuberous sclerosis

## Investigation:

1. CBC: Pancytopenia, ↑↑ MCV, ↑↑ HbF
2. BM examination (aspirate/ biopsy): Hypocellular
3. Chromosomal breakage study
4. Others: Skeletal survey, renal assessment...

#### Inherited causes of chromosomal breakage:

1. Fanconi anemia
2. Ataxia telangiectasia
3. Bloom syndrome
4. Xeroderma pigmentosa

### B) Dyskeratosis congenita (AR)

- Short stature
- Mental retardation
- Skin pigmentation
- Ectodermal dysplasia (Skin pigmentation, nail dystrophy & mucosal leukoplakia)
- Ocular (epiphora & blepharitis)

### C) Amegakaryocytic thrombocytopenia (AR)

**D) Shwachmann-Diamond S (Neutropenia with pancreatic insufficiency) (AR)**

- Metaphyseal chondrodysplasia (short stature)
- Mental retardation
- Pancreatic insufficiency → Malabsorption (steatorrhea) → FTT & short stature
- Neutropenia → pyogenic infection ± Anemia & thrombocytopenia

**Pathology**

1. Pancreas: Atrophy of acini with replacement by **fat** with no fibrosis (Normal islets)
2. BM examination (aspirate/ biopsy): hyporcellular

**Investigation**

1. Fat malabsorption
2. CBC: Neutropenia ± anemia & thrombocytopenia
3. Sweat chloride test: normal

**DD**

1. Cystic fibrosis: pancreatic acinar **fibrosis**, ↑↑ sweat chloride
2. Pearson's S: acinar *fibrosis*, vacuolization of BM precursors & ringed sideroblasts

**Treatment**

1. Pancreatic enzyme replacement
2. Antibiotics
3. GM-CSF or G-CSF
4. BMT

**Seckel syndrome**

- Bird-headed dwarfism
- Hypoplastic face
- Prominent nose
- Low-set ears

**E) Other genetic syndromes: Down syndrome, Seckel syndrome**

## Acquired Aplastic Anemia

**Etiology**

1. Idiopathic (most common)\*\*
2. Irradiation
3. Infection (viruses): CMV, EBV, HBV, HCV, HIV & Parvovirus B<sub>19</sub>
4. Immune: immunodeficiency (Parvovirus B<sub>19</sub>)
5. Drugs
  - a. Predictable: Cytotoxic (chlorambucil), benzene
  - b. Idiosyncrasy: *Antibiotics* (chloramphenicol)  
*Antiepileptics* (phenytoin)  
*Anti-thyroid* (methimazole, PTU)
6. PNH
7. Pregnancy

**Pathogenesis**

1. Direct toxic effect on BM precursors
2. Immune-mediated reaction against BM precursors (Cell-mediated) "↑↑ Cytokines"

**Clinical picture (Pancytopenia)**

- Anemia: Pallor
- Thrombocytopenia: Bleeding
- Leucopenia: Infection (fever)

**Investigations**

1. CBC: pancytopenia, ↑↑ MCV, ↑↑ HbF
2. BM examination (aspirate/ biopsy): hyporcellular
3. Investigation of the cause (hepatitis, PNH...)

**Severe Aplastic anemia =**

BM aplasia or hypoplasia + 2 of:

- ANC < 500/mm<sup>3</sup>
- PLT < 20.000/mm<sup>3</sup>
- Retics < 1%

## Treatment

1. Isolation (if ANC < 500 mm<sup>3</sup>)
2. Diet: high protein & multivitamins
3. Blood transfusion (better from parents or siblings to ↓↓ risk of alloimmunization)
  - Packed RBC: if Hb < 7-9 g % (use irradiated & leukocyte depleted blood)
  - Granulocyte transfusion: for prophylaxis (if ANC < 500/mm<sup>3</sup>) & for Rx of sepsis
  - Platelet transfusion: for prophylaxis (if PLT < 10.000-20.000/mm<sup>3</sup>) & for Rx of Hge
4. Antibiotics: for prophylaxis (SMZ-TMP) & for Rx of infection
5. Rx of acquired aplastic anemia
  - ☒ Immunosuppression
    - Anti-thymocyte globulin (ATG)
    - Cyclosporine
    - Methylprednisolone
  - ☒ GM-CSF or G-CSF (Granulocyte-macrophage colony stimulating factor):  
Used to ↑↑ granulopoiesis in patients with severe neutropenia
  - ☒ BMT (HLA-matched donor)
6. Rx of constitutional aplastic anemia (Fanconi anemia)
  - ☒ Androgen ± steroids  
[Side effects of androgens: hirsutism, acne & hepatotoxicity]
  - ☒ GM-CSF or G-CSF
  - ☒ BMT (HLA matched donor)

## Prognosis

- Mortality in untreated patients = 75% [Hge & infection]
- Long-term-survival = 90% in patients with successful BMT

## Management of Neutopenic Fever

### Definition

- Fever > 38.5°C or 3 elevations > 38°C during 24 hour period
- Neutropenia < 500/mm<sup>3</sup>

### Common Organisms

- Bacteria: G +ve (Staph.aureus, CONS, Streptococci)  
G -ve (Pseudomonas)
- Fungal: Candida & Aspergillus
- Viral: CMV & VZV

### Management

1. Hospital admission & isolation
2. Thorough examination
3. Appropriate cultures & CXR
4. First line antibiotics:
 

Imipenem (Tienam)	Ceftazidime (Fortum)	} ± Aminoglycoside
Meropenem (Meronam)	Cefepime (Maxipime)	
5. Catheter related infection: Vancomycin
6. Perirectal infection: add clindamycin or metronidazole (anaerobes)
7. Persistent fever > one week: Antifungal (Amphotericin B)
8. Total duration of antibiotic therapy: till resolution of infection (usually 10-14 days)

## Disorders of Leukocytes

### Leukocytosis

Total WBC count 2 SD above the mean for age

### Leukopenia

Total WBC count  $< 4.000/\text{mm}^3$

## Neutrophils

### Development

Myeloblast  
↓  
Promyelocyte  
↓  
Myelocyte  
↓  
Metamyelocyte  
↓  
Band  
↓  
Segmented

### Functions

Chemotaxis (LPS, C5a)  
↓  
Attachment (opsonization)  
↓  
Ingestion (phagosome → phagolysosome)  
↓  
Digestion (Intracellular killing)  
-  $\text{O}_2$ -dependent (superoxide  $\text{O}_2^-$ ,  $\text{H}_2\text{O}_2$ , hypochlorous  $\text{HOCl}$ )  
-  $\text{O}_2$ -independent (proteolytic & hydrolytic enzymes)

## Neutrophilia

### Definition

Absolute neutrophil count  $> 12.000/\text{mm}^3$  in the 1<sup>st</sup> day of life  
 $> 8.000/\text{mm}^3$  in adults

### Etiology

1. Infection (Bacterial): pyogenic infections
2. Inflammation: JRA, IBD, Kawasaki
3. Hemorrhage
4. Hemolysis
5. Trauma & surgery
6. Tissue injury (burns)
7. Malignancy
8. Metabolic: DKA, CRF
9. Exercise
10. Epinephrine
11. Leukocyte adhesion deficiency (LAD)
12. Leukemoid reaction: ( $\text{TLC} > 50.000/\text{mm}^3$ )
13. Drugs: GM-CSF, G-CSF & steroids
14. AD form of hereditary neutrophilia
15. Postsplenectomy (& asplenia)

#### Shift to the left:

↑↑ Proportion of band (staff)  
 $\text{Band} / (\text{Band} + \text{Segmented}) > 0.2$

#### Shift to the right:

Hypersegmentation (↓↓ folic &  $\text{B}_{12}$ )

#### Leukemoid reaction

- $\text{WBC} > 50.000/\text{mm}^3$
- ↑↑ Neutrophils
- ↑↑ Activity of WBC ALP

## Neutropenia

### Definition

- Absolute neutrophil count  $< 1.500/\text{mm}^3$
- ☑ Mild neutropenia:  $\text{ANC } 1000\text{-}1500/\text{mm}^3$
  - ☑ Moderate neutropenia:  $\text{ANC } 500\text{-}1000/\text{mm}^3$
  - ☑ Severe neutropenia:  $\text{ANC} < 500/\text{mm}^3$

## Etiology

1. Intrinsic disorders (BM myeloid cells)
2. Extrinsic disorders

## Clinical picture

- Fever, oral ulcers, stomatitis, gingivitis, pharyngitis, sinusitis, OM, cellulites & colitis
- Pneumonia, lung abscess, liver abscess & sepsis
- Mild symptoms & signs of inflammation. Why?

## Investigations

- CBC, ANC, Anti-neutrophil Ab, BM study
- F/U of ANC to exclude cyclic neutropenia

## Treatment

1. Management of infections
2. Granulocyte transfusion, GM-CSF or G-CSF
3. BMT
4. Specific Rx e.g., hypoglycemia, androgens, IVIG, pancreatic enzyme replacement

## Intrinsic disorders causing Neutropenia

	Defect	C/P	Lab
<b>Cyclic neutropenia (AD)</b>	Periodic regular oscillation of ANC ( $\approx 21$ days)	Fever, oral ulcers, stomatitis, pharyngitis, sinusitis, OM, pneumonia, sepsis	$\downarrow\downarrow$ ANC during attacks
<b>Severe congenital neutropenia (Kostmann S)</b>	Arrest of maturation at promyelocytic stage (sporadic)	- Onset = 1 <sup>st</sup> few months Recurrent pyogenic infections (pneumonia...) - Poor prognosis	$\downarrow\downarrow$ ANC ( $< 200/\text{mm}^3$ )
<b>Chronic benign neutropenia (AD/AR)</b>	Mild to moderate neutropenia	No $\uparrow\uparrow$ risk of pyogenic infection	$\downarrow\downarrow$ ANC Normal TLC
<b>Dyskeratosis congenital (AR)</b>		Short stature, MR, pigmentation, Ectodermal dysplasia, Ocular	$\downarrow\downarrow$ ANC
<b>Shwachmann-Diamond S (AR)</b>		Met. Chondrodysplasia, MR Pancreatic insufficiency Neutropenia	$\downarrow\downarrow$ ANC
<b>Cartilage-hair S (AR)</b>		- Short-limb dwarfism - Hair: light, sparse - Immunodeficiency	$\downarrow\downarrow$ ANC X-ray Dysplasia
<b>Chediak-Higashi S (AR)</b>	Defective Degranulation; • PNL • Melanocytes • Platelets	• $\downarrow\downarrow$ ANC (giant PNL granules) • Partial albinism, light skin, silvery hair & photophobia. • Defective Platelet function (bleeding)	$\downarrow\downarrow$ ANC $\uparrow\uparrow$ Bleeding time PLT functions
<b>Hyper-IgM</b>	Defective switch (IgM $\rightarrow$ IgG)	Recurrent bacterial infection	$\downarrow\downarrow$ ANC $\uparrow\uparrow$ IgM $\downarrow\downarrow$ IgG
<b>GSD type Ib</b>	$\downarrow\downarrow$ G-6-P translocase	Hepatomegaly, hypoglycemia, $\uparrow\uparrow$ Uric acid, Cholesterol, Lactate	$\downarrow\downarrow$ ANC $\downarrow\downarrow$ PNL function

## Extrinsic disorders causing Neutropenia

### 1. Infection\*

- Bacterial: Typhoid, TB, Tularemia (*Francisella tularencis*), Pertussis, Brucellosis, sepsis
- Viral\*: CMV, EBV, Viral hepatitis, VZ, MMR (Measles, Mumps, Rubella)
- Fungal: Histoplasmosis
- Protozoal: Malaria, Leishmaniasis
- Rickettsial: Rocky Mountain spotted fever

### 2. Immune:[Anti-neutrophil Ab]

- Autoimmune (analog to AIHA): usually in children with immunodeficiency
- Immune neonatal neutropenia
  - Maternal autoantibodies (Transplacental passage of maternal Ab)
  - Alloimmune (analog to Rh incompatibility & NATP): Maternal Ab

### 3. Irradiation

### 4. Drug-induced (3 mechanisms): Toxic, immune or idiosyncrasy

### 5. Hypersplenism

### 6. BM infiltration

### 7. Nutritional (Folic, B<sub>12</sub> or protein deficiency)

## Eosinophilia

### Definition

Total WBC count 2 SD above the mean for age

### Etiology

#### 1. Allergic disorders: Bronchial asthma, atopy, rhinitis, urticaria, angioneurotic edema

#### 2. Infections:

- Trematodes: Schistosomiasis
- Cestodes: Echinococcus
- Nematodes: Ascaris, Ankylostoma
- Protozoa: Toxoplasmosis, Pneumocystis carinii, Malaria
- Fungi: Aspergillosis

#### Omenn syndrome

- HSM & Lymphadenopathy
- Intractable diarrhea
- Exfoliative erythroderma
- Eosinophilia & ↑↑ IgE

#### 3. Malignancy: AML, eosinophilic leukemia, Hodgkin lymphoma

#### 4. Immunodeficiency: Omenn syndrome, Wiskott-Aldrich, Hyper-IgE syndrome

#### 5. Vasculitis

#### 6. GIT: Eosinophilic gastroenteritis

#### 7. Histiocytosis

#### 8. Tropical eosinophilia: asthma-like symptoms + LN + eosinophilia

Etiology: Helminthes [filaria\*]

#### 9. Loeffler syndrome: Mild respiratory symptoms + Pulmonary infiltrates + eosinophilia

Etiology: Helminthes & Drugs

#### 10. Idiopathic hypereosinophilic S

#### 11. Bronchiolitis obliterans

#### 12. ARDS

#### Idiopathic hypereosinophilic syndrome

##### Diagnostic criteria (Triad)

- Eosinophilia  $\geq 1500/\text{mm}^3 \geq 6$  months
- C/P of organ involvement
- No other diagnoses to explain

##### Clinical Picture:

1. Heart: Restrictive cardiomyopathy
2. Lungs: RD, Pulmonary infiltrates
3. HSM
4. Blood: anemia, thrombocytopenia, eosinophilia
5. Neurologic: Peripheral neuropathy

Prognosis: 75% mortality

Treatment: Steroids & Hydroxyurea



# Hematopoietic Stem Cell Transplantation

## Definition

It is infusion of stem cells into a recipient

## Types

A) Autologous transplantation (from the same individual)

B) Allogeneic transplantation (from other compatible individuals)

1. Bone marrow
2. Umbilical cord blood
3. Peripheral blood stem cells

## Indications

- ALL & AML
- Hodgkin & non-Hodgkin lymphoma
- Thalassemia & Sickle cell anemia
- Neuroblastoma & Wilms
- Aplastic anemia
- Fanconi anemia & Dyskeratosis congenita
- Diamond-Blackfan
- PNH
- Osteopetrosis
- Congenital platelet dysfunction
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Omenn syndrome
- Leukocyte adhesion deficiency (LAD)
- Chronic granulomatous disease (CGD)
- Chediak-Higashi disease
- Hyper IgM syndrome
- Kostmann syndrome
- MPS
- Adrenoleukodystrophy

## Preparation

### ☒ Rationale

- a. Ablation of the patient's BM (either normal or abnormal)
- b. Immunosuppression to allow engraftment (prevention of rejection)
- c. Tumor therapy (in cases of malignancy)

### ☒ Method

- a. High-dose chemotherapy [Cyclophosphamide, Busulfan, Cytarabine...]
- b.  $\pm$  Irradiation

## Post-transplantation (To prevent rejection & GVHD)

Immunosuppressive drugs: Steroids (methylprednisolone), Cyclosporine, Methotrexate

## Evidence of Engraftment

- BM cellularity
- Improved parameters (e.g., immunologic parameters in SCID...)
- Genetic study

SMZ-TMP: for pneumocystis carinii

## Complications

1. Opportunistic infections: prophylactic % therapeutic antimicrobial
2. GVHD (*see immunology*)
3. Graft rejection & graft failure
4. Malignancy
5. HUS, TTP
6. Neurological manifestations due to cranial irradiation or drugs (cyclosporine)
7. Cataract
8. Growth retardation due to irradiation (hypopituitarism), drugs (steroids)
9. Hypothyroidism (primary or secondary)
10. Hypogonadism (primary)

Outcome Depends on 1ry etiology & frequency of previous transfusions [ $\approx$  60-80%]

## Generalized LN Enlargement

### 1. Infections

- a. **Bacterial:** Typhoid, TB, Brucellosis, sepsis
- b. **Viral:** EBV (infectious mononucleosis), CMV, Viral hepatitis, VZ
- c. **Protozoa:** Malaria, Leishmaniasis
- d. **Fungal:** Histoplasmosis
- e. **Rickettsial:** Rocky Mountain spotted fever

### 2. Neoplastic

- a. **Hematologic:** Leukemia, lymphoma (Hodgkin & non-Hodgkin)
- b. **Non-hematologic:** Neuroblastoma

### 3. Immune

- a. Collagen-vascular diseases: Systemic onset JRA & SLE
- b. Immunodeficiency: Chronic granulomatous disease & Chediak-Higashi disease

### 4. Storage diseases

- a. Gaucher
- b. Neimann-Pick

### 5. Drug: Phenytoin

### 6. Miscellaneous: Sarcoidosis, Hyperthyroidism (Graves Disease)

## Cervical LN Enlargement

### 1. Infection

- a. **Bacterial:** Pharyngitis & tonsillitis
- b. **Viral:** URT infection, EBV (infectious mononucleosis), CMV, VZ
- c. **Mycobacteria:** TB & atypical mycobacteria (M. avium, intracellulare, kansaii, marinum)
- d. **Fungal:** Histoplasmosis
- e. **Protozoa:** Toxoplasmosis
- f. **Cat scratch disease:** Bartonella henselae
- g. **Tularemia:** Francisella tularencis

### 2. Neoplastic: Lymphoma, leukemia

### 3. Immune: Kawasaki disease

### 4. Occipital LN: Pediculosis, Rubella, scalp & ear infection

### 5. Generalized Lymphadenopathy

#### Cat-scratch disease:

- Red papule
  - Regional LN
  - FAHM
  - Parinaud oculoglandular S
- Investigations:** ELISA, PCR  
**Rx:** Azithromycin

#### Tularemia: (Zoonotic)

- Ticks, rabbits, rodents
  - Red papule
  - Regional LN
  - FAHM
  - Parinaud oculoglandular S
- Investigations:** ELISA, PCR  
**Rx:** Gentamicin

## Approach to a case of Lymphadenopathy

### (A) History

### (B) Physical examination

### (C) Investigations

#### Indications of LN biopsy

- Persistent or unexplained fever, Weight loss, Night sweating
- Hard or fixed LN
- Associated supraclavicular or mediastinal LN
- ↑↑ Size > 2 wks
- Persistent > 12 wks

# Graft Versus Host Disease

The most common cause of morbidity & mortality after allogeneic HSCT

## Definition

- It is tissue damage caused by engraftment of **immunocompetent** donor's lymphocytes in an **immunocompromised** host with **histocompatibility** difference.
- GVHD usually follows HSCT or simple blood transfusion
- It may be beneficial in cases of graft versus leukemia (GVL)

## Clinical Picture

		Acute GVHD	Chronic GVHD
Onset		7-60 days (< 100 days)	> 100 days
C/P	Skin	Erythematous rash	Sclerodermatous changes
	GIT	Secretory diarrhea	Malabsorption
	Liver	Hepatitis	Cholestasis

## Prevention

1. Proper matching (Histocompatible donors)
2. Post-transplantation immunosuppressive drugs: Methotrexate, Cyclosporine, Steroids
3. Removal of T-cell from the grafts (monoclonal Ab or physical separation)
4. Use of irradiated blood

## Treatment

Immunosuppressive drugs: Steroids (methylprednisolone), ATG

	Iron deficiency	$\beta$ Thalassemia trait	Thalassemia Major	Lead poisoning	Chronic diseases
MCV	↓↓	↓↓	↓↓	↓↓	N or ↓↓
RDW	↑↑	N	↑↑	↑↑	N
HbA <sub>2</sub>	N	↑↑	↑↑	N	N
Iron	↓↓	N	↑↑	N	↓↓
TIBC	↑↑	N	N	N	↓↓
Ferritin	↓↓	N	↑↑	N	↑↑

# **PEDIATRIC NEONATOLOGY**

**By**

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# Introduction

## Neonatal period

The first 28 days of life

## Perinatal period

The period from 28<sup>th</sup> week of gestation till D<sub>28</sub> of life

## Abortion

Termination of pregnancy before **viability** of the fetus

Viability is a reasonable chance of survival (20-28 weeks or  $\geq 500$  g)

## Still Birth

Fetus born dead after viability

## Duration of Pregnancy

280 days = 40 weeks (starting from the 1<sup>st</sup> day of the last menstrual period)

266 from the day of fertilization

☒ 1<sup>st</sup> trimester: 1<sup>st</sup> 12 weeks

☒ 2<sup>nd</sup> trimester: 13-28 weeks

☒ 3<sup>rd</sup> trimester: 28-40 weeks

## Infants are classified as:

- Preterm: delivery before 37 weeks
- Term: 37-42 weeks
- Post-term:  $\geq 42$  weeks

### Placenta

- Shape: Discoid
- Diameter: 15-20 cm
- Weight: 500 gm
- Site: Upper uterine segment

## Antepartum Hemorrhage

☒ **Placenta previa:** Placental implantation over the lower uterine segment

☒ **Accidental hemorrhage:** Premature separation of a normally implanted placenta

## Presentation

The presenting part is the lowermost part of the fetus

- ☒ Cephalic
- ☒ Breech
- ☒ Shoulder

The placenta is normally attached to the upper uterine segment

## Position

The direction of the back of the fetus in relation to the mother

## Lie

The relation between the long axis of the fetus & that of the mother

- ☒ Longitudinal (cephalic & breech)
- ☒ Transverse (shoulder)

## Precipitate Labor

Less than 3 hours

## Prolonged Labor

More than 24 hours

## Fetal membranes

1. **Chorion:** The outer membrane, in contact with the uterine wall, ends at the placental margins
2. **Amnion:** The inner membrane, covers the fetal surface of the placenta & umbilical cord

## Premature Rupture of membranes (PROM)

Rupture of membranes before the onset of labor (Premature & Antepartum)

# Overview of Mortality & Morbidity

## Definition

- ☒ Perinatal mortality: Deaths in the perinatal period
- ☒ Neonatal mortality: Deaths in the neonatal period
- ☒ Infant mortality: Deaths occurring from birth- 12 months
- ☒ Postneonatal mortality: Deaths occurring after the neonatal period & till 1 year of age

## Mortality

### Causes

Fetal	Preterm	Full term
Placental Insufficiency	Severe immaturity, RDS, BPD	Congenital anomalies
Placental separation	IVH	Infection
Umbilical cord accidents	NEC	MAS
Congenital anomalies	Congenital anomalies	PPHN
Congenital infections	Infection	Trauma

## Morbidity

### Causes

System	Immediate	Late
CNS	Hypoxic Ischemic Encephalopathy (HIE) Intracranial hemorrhage (ICH) Seizures Kernicterus Hypotonia	Mental retardation CP (Spastic, choreoathetotic), seizures Learning disabilities Speech & language disorders Microcephaly Hydrocephalus
Hearing & Vision	Retinopathy of prematurity	Hearing & visual impairment Myopia & squint
Respiratory system	Respiratory Failure (RDS) Apnea Pneumothorax	BPD Cor pulmonale Subglottic stenosis Iatrogenic cleft palate
Cardiac	Heart failure PDA (70% if < 1.000 gm)	HTN (Dexamethasone, renal a. stenosis)
GIT	NEC Weak suckling & swallowing	Short bowel syndrome Malabsorption, Malnutrition GERD
Hepatic	Neonatal cholestasis ( <i>sepsis, TPN...</i> ) Indirect hyperbilirubinemia	Cirrhosis Liver cell failure
Renal	ARF ( <i>causes</i> ) ↓↓ Na, ↑↑ Na, ↑↑ K, RTA, glucosuria	Nephrocalcinosis HTN ( <i>renal artery stenosis</i> )
Nutritional	Nutritional deficiencies	Osteopenia, fracture & deformities FTT
Social	Social stress	Child abuse Divorce
Skin	Injury	Scars (PDA, chest tube), Hernia
Infection	Infection	Recurrent infection (pneumonia)
Hematologic	Anemia, Bleeding (↓↓ PLT, DIC, ↓↓ vit.K)	Bleeding sequelae
Metabolic	↓↓ Ca, ↓↓ Glucose Hypo & Hyperthermia	

## High Risk Pregnancies

### Definition

Pregnancies associated with ↑↑ risk of

- ☒ Abortion, IUFD or IUGR
- ☒ Prematurity, congenital anomalies or neonatal disease

### Incidence

- Constitute 10-20% of all pregnancies
- Associated with 50% of all perinatal morbidity & mortality

Identification of high risk pregnancies is important to avoid perinatal morbidity & mortality

### Factors associated with high risk pregnancy

Economic	Reproductive
Poverty Unemployment Uninsured	Previous infant with CP, MR or cong. anomalies Previous infertility Conception by reproductive technology Multiple pregnancies Pre-eclampsia or eclampsia Antepartum hemorrhage (2) Abnormal presentation (breech) or lie (transverse) Abnormal fetal growth AF: Oligohydramnios or polyhydramnios ↑↑ or ↓↓ MSAFP Premature or Post-term labor PROM Prolonged labor CS or instrumental deliveries
Biologic	Maternal Diseases & Drugs
Short stature Malnutrition Poor weight gain during pregnancy Obesity	
Demographic social factors	
Age < 20 or > 35 years Unmarried Physical stress Low educational status Cigarette, alcohol or drug abuse	

## High Risk Infants

### Definition

Infants need to be under close observation (usually for few days)

### Incidence

- Constitute 9% of all pregnancies
- Associated with ↑↑ neonatal morbidity & mortality

Identification of high risk infants is important to avoid perinatal morbidity & mortality

### Etiology (+ high-risk pregnancies)

Previous Pregnancy	Labor & Delivery
Abortion, IUFD or IUGR Prematurity, congenital anomalies or neonatal disease	Prolonged or Precipitate labor Premature baby or post-term baby PROM CS or instrumental deliveries Fetal distress Meconium stained amniotic fluid Low Apgar score
Present Pregnancy	Neonate
Conception by reproductive technology Multiple pregnancies Pre-eclampsia or eclampsia Antepartum hemorrhage (2) Abnormal presentation (breech) or lie Abnormal fetal growth Oligohydramnios or polyhydramnios	Premature or post-term SGA or LGA Pallor, jaundice, cyanosis, tachypnea Congenital anomalies



# Amniotic Fluid

## Production

- ☒ 1<sup>st</sup> half of pregnancy: Secretion by the amniotic epithelium  
Transudation from maternal & fetal circulation
- ☒ 2<sup>nd</sup> half of pregnancy: Fetal urine

## Volume

500-2000 mL

## Function

1. Protection
2. Development of fetal musculoskeletal system "Movement"
3. Growth factors for lung maturation "inhaled by the fetus"



## Abnormalities

	Polyhydramnios	Oligohydramnios
Definition	Amniotic fluid > 2000 ml	Amniotic fluid < 500 ml
Etiology	<ol style="list-style-type: none"> <li>1. Idiopathic* (60%)</li> <li>2. Fetal polyuria (RTA, DI, Bartter)</li> <li>3. Anencephaly, hydrocephalus &amp; meningocele "Leakage"</li> <li>4. Esophageal atresia (TOF)</li> <li>5. Intestinal atresia</li> <li>6. N/M disorders <ul style="list-style-type: none"> <li>• Nerves: SMA type 1 (W.H.)</li> <li>• Muscles: Congenital myopathy</li> </ul> </li> <li>7. DM</li> <li>8. Twin to twin transfusion syndrome</li> <li>9. Achondroplasia</li> <li>10. Hydrops fetalis (Fetal heart failure, anemia, chromosomal...)</li> </ol>	<ol style="list-style-type: none"> <li>1. Idiopathic</li> <li>2. Amniotic fluid leak</li> <li>3. Amnion nodosum (<i>granules on amnion</i>)</li> <li>4. Renal oliguria (agenesis, ARPKD)</li> <li>5. Obst. uropathy (PUV, urethral atresia)</li> <li>6. Twin to twin transfusion syndrome</li> <li>7. Drugs <ul style="list-style-type: none"> <li>• ACE inhibitors</li> <li>• Indomethacin</li> </ul> </li> <li>8. Pulmonary hypoplasia</li> </ol> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <b>Potter syndrome:</b> <ul style="list-style-type: none"> <li>▪ Renal agenesis</li> <li>▪ Oligohydramnios</li> <li>▪ Potter facies: flat nose, micrognathia, low-set ears, limb-positioning defects</li> </ul> </div>

## Examination of Placenta, Cord & Membranes

### A) Placenta

- Placental pallor: Fetal blood loss
- Placental opacity: infection
- Placental edema: Hydrops fetalis (*mention causes*)

**Umbilical cord**  
Length = 50 cm  
Diameter = 1-2 cm

### B) Membranes

- Amnion nodosum
- Oligohydramnios



### C) Cord

- Short cord: may be associated with fetal hypotonia, & chromosomal abnormalities
- Long cord: ↑↑ risk of true knots
- Single umbilical artery: Chromosomal abnormalities (trisomy 18), urinary anomalies
- Meconium staining: Fetal asphyxia
- Whitish nodules on the cord: Candida infection

# The Fetus

Fetal life begins with completion of organogenesis ( $\approx 12$  weeks)

## A) Assessment of Fetal Growth

Method: U/S measurement of

- Biparietal diameter,
- Femur length
- Abdominal cross-sectional area
- Estimated fetal weight

Results:

- ☒ Appropriate for gestational age (AGA)
- ☒ Large for gestational age (LGA)
- ☒ Small for gestational age (SGA) = IUGR

Symmetric (*continuous*)  
[Congenital infection, chromosomal]

Asymmetric (*Late flattening pattern*)  
[Placental insufficiency]

## B) Assessment of Fetal Well being

I Antepartum assessment (= Diagnosis of placental insufficiency)

### 1. Daily fetal movement count

Count of 10: If 10 movements are not counted in 10 hours, the fetus may be at risk

### 2. Non-stress test

Idea: Normally, fetal movements are accompanied by fetal HR acceleration

Technique: Monitoring of FHR in response to fetal movements (Duration = 20 min)

Results:

- ☒ Reactive: 3 criteria;
  - a. FHR = 120-160/min
  - b. Beat-to-beat variability (3-6/min)
  - c. 2 accelerations of  $\geq 15$  beats/min lasting for  $\geq 15$  seconds

☒ Non-reactive  $\rightarrow$  further investigation

### 3. Contraction stress test

Idea: Normally, during uterine contractions there is deceleration of fetal HR.

The onset & the end of deceleration coincide with the onset & end of contraction

Technique: IV infusion of oxytocin to produce uterine contraction

Results:

- ☒ Early deceleration "Normal" [Mirror-image]
- ☒ Late deceleration "Placental insufficiency": Deceleration is prolonged, so the end of deceleration is delayed after the end of contraction

Contraindications: Incompetent cervix, PROM, previous uterine scar

### 4. Biophysical profile (BPP)

	Score = 2	Score = 0
Non-stress test	Reactive	Non-reactive
Fetal movements	$\geq 3$ body/limb movements in 30 min	
Fetal respiratory movements	$\geq 1$ breath movements in 30 min (lasting $\geq 30$ seconds)	
Fetal Tone	$\geq 1$ active extension with return to flexion or hand opening & closure	
Amniotic fluid Vol.*	$\geq 1$ AF pocket $\geq 2$ cm x 2 cm	

Score 8-10

Reassuring  
1 week

Score 6

Equivocal  
48 hours

Score  $\leq 4$

Ominous  
Delivery

### 5. Doppler: Study of blood flow velocity in the umbilical artery

$\downarrow\downarrow$  Blood flow indicates placental insufficiency

## II Intrapartum assessment

### 1. Continuous FHR monitoring (FHR patterns)

FHR & uterine contractions are simultaneously recorded

Normal FHR

Abnormal FHR

- a. Tachycardia (FHR > 160)
  - Early hypoxia
  - Maternal fever, drugs ( $\beta$ -sympathomimetics) & thyrotoxicosis
  - Fetal anemia, arrhythmia
- b. Bradycardia (FHR < 120)
  - Hypoxia
  - Maternal drugs ( $\beta$ -blockers), SLE
  - Fetal arrhythmia (heart block)
- c. Loss of beat-to-beat variability
  - Hypoxia
  - Maternal drugs (narcotics,  $MgSO_4$ )
  - Fetal immaturity
- d. Late deceleration  $\rightarrow$  Fetal hypoxia
- e. Variable deceleration  $\rightarrow$  Cord compression Fetal hypoxia

### 2. Fetal scalp blood sampling

Using vaginal speculum, lancet & capillary tube

- a. pH  $\geq 7.25 \rightarrow$  Normal
- b. pH 7.2-7.25  $\rightarrow$  Borderline
- c. pH  $\leq 7.2 \rightarrow$  Fetal hypoxia (*anaerobic metabolism*)

### 3. Fetal scalp pulse oximetry

### 4. Passage of meconium in cephalic presentation $\rightarrow$ Fetal hypoxia

#### Normal FHR:

1. Rate 120-160/min
2. Beat-to-beat variability (3-6)
3.  $\uparrow\uparrow$  with fetal movement
4.  $\downarrow\downarrow$  with uterine contractions (Early deceleration)

## Causes of Intrauterine Asphyxia

### A) Maternal causes

- Cardiac: Heart failure, Shock
- Respiratory failure
- Severe anemia
- Hypotension (blood loss)
- Eclampsia (convulsions)

### B) Placenta (Placental insufficiency) $\rightarrow$

### C) Cord

- Compression (fetal head, forceps)
- Prolapse
- Ruptured vasa previa

### D) Compression of fetal head

- Pelvis (Cephalo-pelvic disproportion)
- Forceps
- ICH, depressed fracture

#### Causes of Placental Insufficiency

- ☒ **Acute:** Placental separation (Placenta previa & accidental Hge)
- ☒ **Chronic:**
  - Pregnancy-induced HTN (Pre-eclampsia)
  - Chronic HTN
  - Advanced DM
  - Placental infarction
  - Placental aging (Post-term)
  - Sickle cell anemia
  - Smoking
  - Drugs: cocaine
  - Idiopathic

Diagnosis: see before

C/P: IUGR, IUFD

Diagnosis: see before

Rx: Immediate delivery

Positioning (on the Lt Side) + oxygen supplementation

Surfactant/Albumin ratio in AF

**C) Assessment of Fetal Functional Maturity****a. Renal functional maturation: Amniotic fluid creatinine level**

Early in pregnancy, AF creatinine is equal to maternal serum creatinine

By 37 wks, AF creatinine: Maternal serum creatinine is  $\geq 3$ **b. Lung functional maturation: Lecithin/ Sphingomyelin ratio (and S/A ratio)**In the 3<sup>rd</sup> trimester, L/S = 1By 35 wks, L/S = 2 (Indicates lung maturity with  $\downarrow\downarrow$  risk of development of RDS)**D) Effects of Maternal Diseases on the Fetus**

System	Maternal Disease	Effect
CVS	CHD, RHD, HF	IUGR (Placental insufficiency)
	HTN	IUGR (Placental insufficiency)
	PIH	IUGR (Placental insufficiency)
CNS	Myasthenia gravis	Transient neonatal myasthenia (Transplacental Ab)
	Myotonic dystrophy	Myotonic dystrophy (Genetic, AD, anticipation)
Hematologic	ITP, SLE	Neonatal thrombocytopenia (Transplacental Ab)
	NATP	Neonatal thrombocytopenia (Transplacental Ab)
	Sickle cell anemia	IUGR (Placental insufficiency)
Collagen	SLE (or Sjogren)	Fetal & neonatal heart block (Transplacental Ab)
Metabolic	Phenylketonuria (PKU)	Microcephaly, MR ( $\uparrow\uparrow$ Maternal phenylalanine)
Endocrine	DM	LGA (Fetal hyperglycemia & hyperinsulinemia) Neonatal hypoglycemia IUGR (Placental insufficiency & Vascular disease)
	Graves disease	Transient neonatal thyrotoxicosis (Transplacental Ab)
	Endemic goiter	Hypothyroidism (iodine deficiency)
	Hyperparathyroidism	Neonatal hypocalcemia (Fetal hypercalcemia)
	Hypoparathyroidism	Neonatal hypercalcemia (Fetal hypocalcemia)
Nutritional	Obesity	LGA & Neonatal hypoglycemia
	Malnutrition	IUGR ( $\downarrow\downarrow$ fetal nutrients)

**Teratogens****Definition**

Teratogen is any environmental agent (drug, substance or exposure) that interferes with normal embryonic development (structure, growth or function)

**Examples:**

- Drugs
- Infection
- Maternal diseases DM & PKU
- Radiation (ionizing & non-ionizing)

Mechanism of teratogens
1. DNA damage
2. Cell death
3. Vascular insult
4. Delayed differentiation

**Effect** The effect depends on:

- ☒ Nature of the teratogen (*The mechanism is usually unknown*)  
Warfarin is teratogenic on fetal cartilages [ $\#$  carboxylation of glutamic acid]
- ☒ Time of exposure (fetal age)
  - a. Weeks 1-3 (embryonic stage): All or none fashion; either killing or no effect
  - b. Weeks 3-10 (organogenesis): organs are most susceptible to damage
  - c. Weeks 10-40 (fetal growth & maturation):  $\downarrow\downarrow$  risk but may interfere with function
- ☒ Genetic predisposition: teratogens are not universal "Pharmacogenetics"

## E) Effects of Maternal Medications on the Fetus

### 1. Drugs affecting the fetus & newborn

	Drug	Effect
1	Alcohol	IUGR
2	Amphetamine	IUGR
3	Caffeine	IUGR, Abortion
4	Cigarette smoking	IUGR
5	Cocaine	IUGR, microcephaly
6	ACE inhibitors (Captopril)	Renal impairment, Oligohydramnios
7	Indomethacin	Renal impairment, Oligohydramnios
8	Mercury	MR, microcephaly
9	Methyltestosterone	Masculinization of the ♀ fetus
10	Progesterone	Masculinization of the ♀ fetus
11	Propranolol	Fetal bradycardia
12	Sympathomimetics (tocolytics)	Fetal tachycardia
13	Propylthiouracil	Goiter
14	Phenytoin	Congenital anomalies, bleeding (anti-Vit. K)
15	Valproate	Congenital anomalies, spina bifida
16	Streptomycin	Deafness
17	Tetracycline	Enamel hypoplasia, pigmentation of teeth
18	Thalidomide	Phocomelia
19	Vitamin D	Supravalvular aortic stenosis
20	Warfarin	Bleeding, cartilage anomalies

### 2. Drugs affecting the newborn

	Drug	Effect
1	Anesthesia	CNS depression
2	MgSO <sub>4</sub>	Respiratory depression
3	ACE inhibitors (Captopril)	Renal impairment, oliguria
4	Indomethacin	Renal impairment, oliguria, bleeding, perforation
5	Aspirin	Bleeding, perforation
6	Oxytocin	Hyperbilirubinemia, Hyponatremia
7	Vitamin K	Hyperbilirubinemia
8	Sulfonamide	Hyperbilirubinemia, hemolysis in G6PD deficiency
9	Primaquine (anti-malarial)	Hemolysis in G-6-PD deficiency
10	Nitrofurantoin	Hemolysis in G-6-PD deficiency
11	Iodide (Amiodarone)	Neonatal goiter
12	Lead	↓↓ intellectual functions
13	Propranolol	Neonatal bradycardia & hypoglycemia
14	Sympathomimetics (tocolytics)	Neonatal tachycardia
15	Sulfonylurea	Hypoglycemia

## F) Fetal Diagnosis & Therapy

### I Antenatal Diagnosis

#### 1. Maternal serum $\alpha$ -fetoprotein (MSAFP)

- ☒  $\downarrow\downarrow$  MSAFP: Down syndrome & other trisomies
- ☒  $\uparrow\uparrow$  MSAFP: Neural tube defects (anencephaly, encephalocele, spina bifida)
  - Hydrocephalus
  - GIT: TOF, Intestinal atresia
  - Renal: Congenital nephrosis, Obstructive uropathy
  - Twins, IUFD

#### 2. Fetal US

- ☒ Assessment of fetal growth & gestational age
- ☒ Assessment of fetal well-being (e.g., BPP, Doppler study of the umbilical artery...)
- ☒ Nuchal Translucency thickening (NT): thickening of the fat pad at the back of the neck
- ☒ Dilated cerebral ventricular system (hydrocephalus)
- ☒ Dilated renal pelvicalyceal system [large UB in PUV]
- ☒ Absent stomach (TOF), Double-bubble (duodenal atresia), Distended loops (IO)
- ☒ Fetal echocardiography
- ☒ Obstetric applications:
  - Diagnosis of pregnancy & multiple pregnancies
  - Estimation of gestational age
  - Localization of the placenta, AF volume.
  - Diagnosis of position, presentation & lie

#### 3. Amniocentesis & Chorionic Villus Sample (CVS)

	Amniocentesis	Chorionic villus sample
Timing	2 <sup>nd</sup> Trimester (14-16 weeks of gestation)	1st Trimester (9-12 weeks of gestation)
Anesthesia	LA or GA	LA or GA
Technique	Transabdominal or transvaginal sample of amniotic fluid (US guided)	Transvaginal transcervical biopsy of chorionic villi (US guided)
Obtained Cells	1. Fetal sexing (XL diseases e.g., hemophilia, Duchenne ...) 2. Karyotyping (chromosomal abnormalities e.g., Down, trisomies...) 3. DNA analysis (Thalassemia, Sickle cell disease, cystic fibrosis...) 4. Enzyme assay (Galactosemia, GSD, Gaucher, Niemann-Pick, MPS, GM <sub>1</sub> , GM <sub>2</sub> )	
Liquid phase (in amniocentesis)	1. $\alpha$ -fetoprotein (causes as MSAFP) 2. Bilirubin (Erythroblastosis fetalis) 3. Lung maturity (L/S ratio...) 4. Renal maturity (creatinine) 5. CAH ( $\uparrow\uparrow$ Ketosteroids) 6. Congenital hypothyroidism ( $\downarrow\downarrow$ T <sub>4</sub> )	??
Complications	▪ Abortion ▪ Fetal injury ▪ Hemorrhage ▪ Rh sensitization ▪ Infection (amnionitis)	▪ Abortion (2% higher) ▪ Amnion puncture ▪ Hemorrhage ▪ Rh sensitization ▪ Infection
Pros & Cons	▪ Less risk of abortion ▪ Technically easier ▪ $\downarrow\downarrow$ yield of cells (cells must be cultured)	▪ $\uparrow\uparrow$ yield of cells (rapid diagnosis) ▪ Early in pregnancy (when termination is less risky & less emotionally traumatic)

#### 4. Fetoscopy & Fetal Tissue Sampling

Transabdominal introduction of fetoscope under LA (US guided), 2<sup>nd</sup> trimester

- Direct visualization (structural anomalies e.g., phocomelia, neural tube defects...)
- Cordocentesis (Fetal blood sampling)
  - Hemoglobinopathies: Sickle cell anemia
  - Coagulation disorders (Hemophilia)
  - Neonatal alloimmune thrombocytopenia
  - Fetal infection (Toxoplasmosis)
  - Immunodeficiency
  - Karyotyping, DNA analysis & enzyme assay
- Fetal liver biopsy (PKU & OTC deficiency)
- Fetal skin biopsy (epidermolysis bullosa)

OTC = Ornithine transcarbamoylase  
Most common type of urea cycle defects  
XL-R    الوحيد

#### 5. Pre-implantation genetic diagnosis (PGD)

### II Fetal Therapy

System	Fetal Disease	Treatment
CVS	SVT	Maternal digitalis, amiodarone
	Heart block	Pacemaker
CNS	Hydrocephalus	Shunt ( <i>Ex-utero inpartum</i> )
	Neural tube defects	Folic acid supplementation (Prevention)
Hematologic	Anemia with <u>Hydrops</u>	Packed RBC (Umbilical vein)
	Thalassemia	Stem cell transplantation
	Maternal ITP & SLE	Maternal IVIG & steroids
	NATP	Maternal IVIG & Platelet transfusion (Umbilical vein)
	Chronic granulomatous disease (CGD)	Stem cell transplantation
Respiratory	SCID	Stem cell transplantation
	Lung immaturity	Maternal dexamethasone
Metabolic	Hypoxia (& IUGR)	Maternal oxygen & position
	Maternal PKU	Maternal phenylalanine restriction
Endocrine	Fetal Galactosemia	Maternal Lactose free diet
	DM	Maternal glycemic control
	Graves disease	Maternal Propylthiouracil
	Endemic goiter	Fetal Hypothyroidism (Intra-amniotic thyroxine)
Amniotic fluid	CAH	Maternal dexamethasone (When??)
	Oligohydramnios	Amnioinfusion
Renal	Polyhydramnios	Amnioreduction
	Obstructive Uropathy	Vesicoamniotic shunt
Infections	Bartter syndrome	Maternal Indomethacin therapy
	GBS	Maternal ampicillin (Prevention)
	CMV	Gancyclovir (Umbilical vein)
	HIV	Zidovudine
	Toxoplasmosis	Spiramycin, pyrimethamin, Sulfadiazine, Folic
	TB	Anti-TB drugs
TTTS	Lyme, Syphilis	Penicillin
		YAG Laser photocoagulation of shared vessels

### III Prevention of Fetal & Neonatal Disease

1. Folic acid supplementation ↓↓ risk of neural tube defects (NTDs): 400 µg/day
  - ♀ without previous history of NTDs: 400 µg/day
  - ♀ with previous history of NTDs or +ve family history: 4 mg/day
2. Anti-D for prevention of erythroblastosis fetalis
3. Steroids for prevention of RDS
4. MMR vaccine to all ♀ before the age of 12 yrs (pregnancy should be avoided for 3 m)
5. Tetanus toxoid for prevention of neonatal tetanus
6. Rx of maternal diseases
  - Infections: Syphilis, UTI...
  - Noninfectious: control of DM, PKU, ITP...
7. Fetal transfusion
  - Blood: immune hydrops
  - Platelet: Neonatal alloimmune thrombocytopenic purpura
8. Prevention of prematurity
  - Antenatal care for early diagnosis & Rx of causes of prematurity (PIH, PN, DM...)
  - Avoid stress, heavy work
  - Rest & proper diet
  - Tocolytics (Ritodrine...) & Cerclage operation

### G) Assessment of Gestational Age

#### Importance

- a. Proper assessment of fetal growth, fetal well being & fetal functional maturity
- b. Proper timing of antenatal diagnostic procedures (amniocentesis & CVS)
- c. Proper timing of elective obstetric procedures (elective CS)
- d. Identification of premature delivery (? neonatal management)

#### Methods

- a. History: 1<sup>st</sup> day of the last menstrual period (LMP)
- b. Examination: Fundal level
- c. U/S
  - 1<sup>st</sup> trimester: Crown-rump length
  - 2<sup>nd</sup> trimester: Biparietal diameter & femur length

1. Fetal Growth
2. Fetal well being
3. Fetal functional maturity
4. Maternal Diseases
5. Maternal Medications
6. Fetal Diagnosis, Rx & prevention
7. Gestational Age

NB:

### Classification of Teratogens (Teratogenic Drugs)

	Risk	Based on??
Category A	No risk	Human trials
Category B	No risk	Animal trials
Category C	Risk	Animal trials (No adequate human trials)
Category D	Risk (Benefits > Risk)	Human or Animal trials
Category X	Contraindicated (Risk > Benefits)	Human or Animal trials

### Prevention of Teratogenesis

- Avoid drugs, infection & radiation
- Control of maternal DM, PKU
- Abortion



# Neonatal Examination

## Examination in the Delivery Room

### 1. Color

☒ Cyanosis

- Central: Respiratory, cardiac, CNS or methemoglobinemia
- Peripheral (acrocyanosis): Hypothermia
- Differential: ↑↑ Pulmonary vascular resistance

☒ Pallor

- Anemia
- Hypoxia
- Edema

☒ Jaundice (rare in the delivery room)

☒ Meconium staining

### 2. Respiration

☒ RD (Tachypnea, retraction, grunting, cyanosis)

☒ Bradypnea (CNS depression)

☒ Stridor (Partial obstruction at the level of upper airways)

☒ Auscultation (air entry- ? intestinal sounds)

### 3. CVS

☒ Heart (rate & murmurs)

☒ Peripheral pulses

### 4. Abdomen

☒ Scaphoid abdomen (Diaphragmatic hernia)

☒ Organomegaly (Congenital infection & metabolic)

☒ Cord examination (long, short, single umbilical artery)

### 5. Genitalia

☒ Sex of the baby

☒ Atypical genitalia (ambiguous)

### 6. Gastric aspiration: ↑↑ in IO (> 30 cc)

### 7. Choanal atresia: using suction catheter

### 8. Imperforate anus: using the same catheter

### 9. Congenital anomalies: e.g., meningocele...

### 10. Apgar score: assigned at 1, 5 minutes ± 10 & 20 minutes

It is a practical method for assessment of newborns during the 1<sup>st</sup> few minutes of life

Sign	0	1	2
Heart rate*	Absent	< 100	> 100
Respiration*	Absent	Slow, irregular	Good, crying
Tone	Limp	Some flexion	Active movements
Reflex to suction	No response	Grimace	Cough, sneeze, crying
Color*	Blue or pale	Pink body, blue extremities	Pink

Apgar at 1 minute is an index of inpartum asphyxia & need for resuscitation

Apgar at 5 minutes is used to assess the efficiency of resuscitation

Apgar at 15 & 20 minutes is used to determine the prognosis

Monitoring during resuscitation is used by assessing respiration, HR & color (every 15-30 sec)

#### Abdominal mass in a neonate:

##### 1. Renal

- ARPKD, ADPKD
- MODK
- Hydronephrosis
- Renal vein thrombosis
- Wilms tumor

##### 2. Adrenal Hge

##### 3. Neuroblastoma & hepatoblastoma

##### 4. Hydrometrocolpos

##### 5. Cysts

- Mesenteric
- Choledochal
- Ovarian
- Pancreatic

##### 6. HSM

## Examination in the Nursery

### A) Vital Signs

#### 1. Temperature (axillary)

Avoid hypothermia during examination (radiant warmer)

Estimated heat loss in neonates is 4 times that of an adult

#### 2. Respiratory rate

- ☒ Rate = 30-60/minute
- ☒ Rhythm: regular (periodic breathing is normal during sleep)
- ☒ Signs of RD (Tachypnea, retraction, grunting, cyanosis)
- ☒ Bradypnea (CNS depression)
- ☒ Stridor (Partial obstruction at the level of upper airways)
- ☒ Auscultation (air entry-bronchovesicular- ? intestinal sounds)

HR & RR should be counted over 1 minute

#### 3. Heart rate

- ☒ Rate = 120-160/minute [Range = 90 (sleep)- 180 (crying)]
- ☒ Peripheral pulses

#### 4. Blood pressure

- ☒ Normal  $\approx$  80/40 (mean BP = 40-50 mmHg)
- ☒ Method: auscultatory or automated (DINAMAP)
- ☒ In UL & LL (Coarctation)

Device for Indirect Noninvasive Automated Mean Arterial Pressure

### B) Anthropometric Measurements

- 1. Length  $\approx$  50 cm
  - 2. Weight  $\approx$  2.500-3.999 Kg
  - 3. Skull circumference  $\approx$  35 cm
- } Growth curves

### C) Systemic Examination

#### 1. Skull

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> Molding (overlapping sutures) | <input checked="" type="checkbox"/> Large AF (hydrocephalus, hypothyroidism) |
| <input checked="" type="checkbox"/> Cephalhematoma                | <input checked="" type="checkbox"/> Open Post. Fontanel                      |
| <input checked="" type="checkbox"/> Caput succedenum              | <input checked="" type="checkbox"/> Microcephaly                             |
| <input checked="" type="checkbox"/> Depressed fracture            | <input checked="" type="checkbox"/> Microcephaly                             |

#### 2. Eyes

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Lid swelling: infection, irritation | <input checked="" type="checkbox"/> Lens: Cataract                        |
| <input checked="" type="checkbox"/> Upward slanting: Down               | <input checked="" type="checkbox"/> Glucoma (blue sclera)                 |
| <input checked="" type="checkbox"/> Cornea: opacities                   | <input checked="" type="checkbox"/> Iris: Coloboma (Key-shaped pupil)     |
| <input checked="" type="checkbox"/> Conjunctiva: Subconjunctival Hge    | <input checked="" type="checkbox"/> Fundus: chorioretinitis (TORCH) & Hge |

White pupil reflex:  
1. Cataract  
2. Glaucoma  
3. Retinoblastoma

#### 3. Ears

- ☒ Assessment of gestational age (cartilage)
- ☒ Abnormal shape (congenital anomalies)
- ☒ Low set ears: Helix meets the cranium at lower level (horizontal level of inner canthi)

#### 4. Nose

- ☒ Choanal atresia (RD, Obligatory nose breathers, Crying...)
- ☒ Flattening: Potter's facies

#### 5. Mouth

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Tongue tie                         | <input checked="" type="checkbox"/> Natal tooth (remove if loose to avoid aspiration) |
| <input checked="" type="checkbox"/> Excessive drooling of saliva (TOF) | <input checked="" type="checkbox"/> Cleft palate                                      |
| <input checked="" type="checkbox"/> Lingual thyroid                    | <input checked="" type="checkbox"/> High arched palate                                |

#### 6. Jaw: Micrognathia (Pierre-Robin syndrome)

#### 7. Face: facial palsy, trisomies, dysmorphism...

## 8. Neck

- ☒ Webbing (Turner)
- ☒ Goiter
- ☒ Sternomastoid tumor
- ☒ Fracture clavicle

## 9. Chest

- ☒ Nipples (widely separated in Turner)
- ☒ Areola (assessment of gestational age)
- ☒ Deformities (pectus excavatum & carinatum)
- ☒ Intestinal sounds (Diaphragmatic hernia)

## 10. Heart

- ☒ HR = 120-160
- ☒ Murmurs

Hart murmur may be CHD (*chance is 1:12*)  
Innocent murmurs are **much more frequent**

The most common innocent murmur in neonates  
**pulmonary flow murmur**

## 11. Abdomen

- ☒ Scaphoid (Diaphragmatic hernia)
- ☒ Ascite (Urinary ascites, chylous...)
- ☒ Abdominal mass (DD: *mention*)
- ☒ Absent abdominal wall muscles (Prune-Belly \$)
- ☒ Liver, tip of spleen & lower pole of the kidney  
(may be *normally* felt)

## 12. Genitalia

- ☒ Hypospadias (avoid circumcision)
- ☒ Atypical genitalia (CAH)
- ☒ Interrupted urine stream (PUV)
- ☒ Penile erection is normal

## 13. Back

- ☒ Meningomyelocele
- ☒ Spina bifida occulta (lipoma, tuft of hair, sinus...)

## 14. Extremities (musculoskeletal system)

- ☒ Absent radius (TAR)
- ☒ Thumb anomalies (Fanconi anemia)
- ☒ Talipes
- ☒ Erb's palsy & fractures
- ☒ Polydactyly, syndactyly
- ☒ DDH (developmental dysplasia of the hip)
- Routine tests: Barlow & Ortolani →



## 15. Skin

- ☒ Pallor, jaundice, cyanosis, plethora
- ☒ Lanugo hair: ↑↑ in preterm babies
- ☒ Vernix caseosa: white, greasy, waxy substance covering the skin (↑↑ in preterm babies)
- ☒ Macular hemangioma: usually on the upper eyelids, bridge of the nose & forehead
- ☒ Milia: small yellowish white papules over the nose & cheeks (disappear within weeks)
- ☒ Mongolian spots: Bluish areas of pigmentation over the back & buttocks (disappear 1-2 yrs)
- ☒ Erythema toxicum: erythematous macules, papules & vesicles usually on the trunk.  
Contains eosinophils (? allergic). Cultures are sterile.
- ☒ Transient pustular melanosis: vesiculopustular eruption in the chin, neck, palms & soles.  
Contains PNLs. Cultures are sterile.
- ☒ Edema (*causes of hydrops*)
- ☒ Hyperpigmentation: CAH, Fanconi anemia, café-au-lait spots, McCune-Albright \$
- ☒ Hypopigmentation: Albinism, tuberous sclerosis, Chediak-Higashi \$
- ☒ Neurocutaneous syndromes: NF, TS, Sturge-Weber
- ☒ Scaly skin lesions: ichthyosis, acrodermatitis enteropathica
- ☒ Vesiculobullous diseases: epidermolysis bullosa
- ☒ Dermal sinuses: thyroglossal, preauricular, pilonidal & branchial sinus

## 16. Anus & Rectum

- ☒ Patency should be checked
- ☒ Passage of meconium

## 17. Neurologic

- ☒ Full neurologic examination
- ☒ Neonatal reflexes

## 18. Assessment of Gestational age

### Assessment of gestational age—new Ballard score.

#### Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)							
Arm recoil							
Popliteal angle							
Scarf sign							
Heel to ear							

#### Physical Maturity

Skin	Slick, shiny, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	Maturity Rating
Plantar surface	Heel-toe 40-60 mm; -1 < 40 mm; -2	> 50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	Score Weeks
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Slipped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	-10 20
Eye/Ear	Lids fused loosely; -1 tightly; -2	Lids open; pinna flat; stays folded	Slightly curved pinna, soft; slow recoil	Well curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	-5 22
Genitalia (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	0 24
Genitalia (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minor	Clitoris prominent, enlarging minor	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	5 26
							10 28
							15 30
							20 32
							25 34
							30 36
							35 38
							40 40
							45 42
							50 44

Scores from neuromuscular and physical domains are added to obtain total score.

Neuro-muscular system	physical
Posture	Skin
Square window	Lanugo
Arm recoil	Plantar creases
Scarf sign	Breast
Popliteal angle	Eye/ear
Heel to ear	Genitalia (♂ & ♀)

## Nursery Care of the Well Newborn

### 1. Hand Washing (using Sterillium)

### 2. Maintenance of body Temperature

- Skin-to-skin with the mother (Kangaroo care)
- Radiant warmer (servo control)

### 3. Check

- ☒ Vital signs (RD)
- ☒ Color (Pallor, cyanosis, jaundice)
- ☒ Jitteriness ( $\downarrow\downarrow$  glucose,  $\downarrow\downarrow$  Ca)

### 4. Care of the skin

- Sterile cotton soaked with fresh warm tap water to remove blood, meconium
- 1<sup>st</sup> bath is delayed till stabilization of temperature

### 5. Care of the cord (using Alcohol 70%)

### 6. Care of the Eye (prophylactic eye drops)

### 7. Vitamin K (0.5-1 mg IM\*, alternatively, several oral doses may be given)

### 8. Complete physical examination (vital signs, measurements, systemic, gestational age)

### 9. Urine & Stools

### 10. Immunization (BCG & HBV $\pm$ HBIG)

### 11. Neonatal screening

- Hypothyroidism, Galactosemia, PKU & Hemoglobinopathies
- Medium chain acyl-CoA dehydrogenase (MCAD)
- Cystic fibrosis (in UK)

### 12. Hearing screen (for congenital hearing loss)

### 13. Glucose screening (for IDM, LGA & SGA)

### 14. Bilirubin screening (serum or transcutaneous measurement)

### 15. Cord blood (can be saved for 2 wks): Blood group & Coombs test

- Rh -ve mother
- Neonatal jaundice in the 1<sup>st</sup> 24 hrs
- Previous infant with Coombs positive hemolytic anemia

### 16. Circumcision

Benefits:  $\downarrow\downarrow$  UTI, cancer penis & STDs

Complications: Bleeding & infection (*bleeding profile is required if +ve family history*)

Contraindications: Hypospadias, ambiguous genitalia, unstable clinical status

Analgesia: Nerve block & EMLA cream (*Sucrose 24% pacifier is used as adjuvant*)

### 17. Early Feeding

- Breastfeeding should be initiated ASAP preferably in the delivery room (8-12 times/day)
- Artificial feeding: every 3-4 hours

### 18. Discharge & Follow-up

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> NVD</li> <li><input checked="" type="checkbox"/> Uncomplicated delivery</li> <li><input checked="" type="checkbox"/> Singleton, FT, AGA</li> <li><input checked="" type="checkbox"/> Stable vital signs in open cot <math>\geq</math> 12 hr</li> <li><input checked="" type="checkbox"/> Urine, stool <math>\geq</math> 1</li> <li><input checked="" type="checkbox"/> Feeding <math>\geq</math> 2</li> <li><input checked="" type="checkbox"/> Normal physical examination</li> </ul> | <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> No NJ in the 1<sup>st</sup> 24 hr</li> <li><input checked="" type="checkbox"/> No excessive post circumcision bleeding</li> <li><input checked="" type="checkbox"/> Completion of metabolic screening</li> <li><input checked="" type="checkbox"/> Vaccination (HBV)</li> <li><input checked="" type="checkbox"/> Maternal competence in routine neonatal care</li> <li><input checked="" type="checkbox"/> No social risk (teen mother, history of child abuse)</li> <li><input checked="" type="checkbox"/> F/U arrangement</li> </ul> |
|---|---|

#### Criteria for admission to the nursery:

1. Well-appearing neonate
2.  $\geq$  35 weeks
3.  $\geq$  2 Kg

Healthy newborns should be with their mothers all or near all the time

Urine: 1<sup>st</sup> 30 hours  
Meconium: 1<sup>st</sup> 48 hours

Infants born to HBsAg +ve mother should receive both HBV & HBIG within 12 hr

# Breastfeeding

## Advantages

### A) To the mother

1. Prevention of postpartum He (oxytocin)
2. Contraceptive value
3.  $\downarrow\downarrow$  Risk of breast cancer & osteoporosis
4. Economic

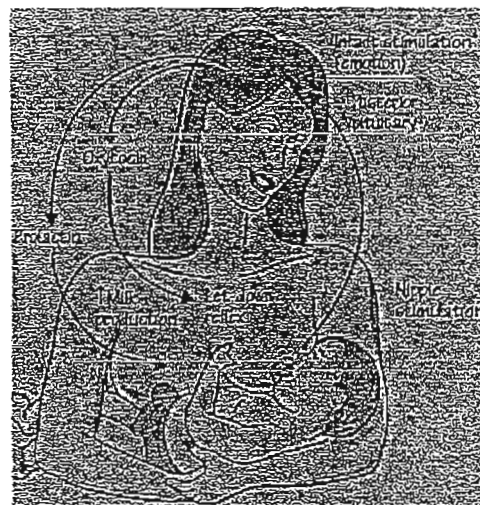
### B) To the Baby

1. Psychological (Mother-infant bonding)
2.  $\downarrow\downarrow$  Risk of atopy, obesity, type 1 DM
3.  $\downarrow\downarrow$  Incidence of NEC
4.  $\uparrow\uparrow$  IQ
5. GIT growth factors
6. Anti-infective properties

- Sterile
- IgA (Surface immunity)
- Lysozyme (Dissolves bacterial cell wall)
- Lactoferrin (Binds iron & B<sub>12</sub>)

#### 7. Nutritional

- High nutritive value
- Proper unique composition



**Breast is the best**

- Anti-Staph. Factor
- Lactobacillus bifidus promoting factor  
→  $\uparrow\uparrow$  Lactobacilli →  $\downarrow\downarrow$  E.coli
- Cells: lymphocytes & macrophages

Item	Composition	Comments	Preterm Breast milk
Energy	67 Kcal/dL		67 Kcal/dL
Proteins	1.25 g/dL	Whey predominant (4:1)	1.8-2.4 g/dL
CHO	7 g/dL	Lactose	6 g/dL
Fat	3.9 g/dL	$\uparrow\uparrow$ content of essential FA	3.9 g/dL
Ca	28 mg/dL	Ratio 2:1 is optimal for absorption.	15 mg/dL
P	14 mg/dL		14 mg/dL
Na	7 mEq/L	Breast milk has a lower Na content	22 mEq/L
K	15 mEq/L		18 mEq/L
Iron	0.03 mg/dL	Iron stores are sufficient for 2 m	
Vitamin A	225 IU/dL		
Vitamin D	2 IU/dL		
Vitamin E	0.4 IU/dL		

## 10 Steps for Successful Breastfeeding

1. Have a written policy
2. Training of health care providers
3. Educate all pregnant mothers (Benefits)
4. Help to initiate breastfeeding within 1/2 hr
5. Show how to breast-feed
6. Rooming-in (mother & infant together)
7. Exclusive
8. On demand feeding
9. No pacifiers
10. Breastfeeding support groups

Hind milk contains more fat than foremilk

## Expression & Storage of Breast Milk

- ☑ Hand washing
- ☑ Sterilization of milk collection equipment
- ☑ Expression using a pump
- ☑ Plastic containers are usually used
- ☑ Labeling the container with the name & date
- ☑ The amount should be suitable for single feed

▪ Fresh unrefrigerated milk	1 hour
▪ Stored fresh (4°C)	1-2 days
▪ Freezing	6 months

## Contraindications of Breastfeeding

1. Inborn errors of metabolism: Galactosemia & PKU
2. Breast milk jaundice
3. Maternal infection
  - ☑ Open TB (Expressed breast milk can be given)
  - ☑ CMV in extremely preterm babies
  - ☑ HIV
  - ☑ Human T Cell Lymphotropic Virus (HTLV-1 & HTLV-2)
4. Maternal medications

Conditions that are Not CF
▪ HCV (No evidence of milk transmission)
▪ HBV (Give HBV + HBIG)
▪ Fever
▪ Smoking (But advise the mother)

Most drugs are secreted in breast milk in small amount that do not affect the baby  
Whenever possible, all drugs should be avoided during breastfeeding

Contraindicated	Avoid or give with caution	Probably Safe
Antineoplastics	Aspirin	Acetaminophen
Amiodarone	Alcohol	Antibiotics
Bromocriptine	OCPs	Antiepileptics
Cyclophosphamide	Estrogen	Anesthetics
Cocaine	Laxatives	Antihistaminics
Chloramphenicol	Metoclopramide	Diuretics
Diethylstilbestrol		Digoxin
Ergots		Theophylline
Heroin		Insulin
Lithium		Prednisone
Methotrexate		Propylthiouracil
Methimazole		Propranolol
Radioactive Iodine		Vitamins
Tetracycline		Warfarin

## Disadvantages of Breastfeeding

- ☑ Amount taken by the baby can not be determined
- ☑ Breast milk jaundice
- ☑ Without fortification, breast milk is not suitable for preterm
- ☑ Breast engorgement, fissured nipple & mastitis
- ☑ Transmission of some diseases (HIV, CMV, HTLV, GBS, *Listeria monocytogenes*)

Premature neonates require more proteins, Ca & PO<sub>4</sub>

## Colostrum

- Breast milk in the 1<sup>st</sup> 2-3 days
- Daily amount = 60 cc
- High protein content = 8 g/dL
- Value: nutritive (↑↑ proteins) & protective (IgA)

# Prematurity

## Classification of Newborns

### A) Gestational age classification

- Preterm: delivery before 37 weeks
- Term: 37-42 weeks
- Post-term:  $\geq 42$  weeks

### B) Birth weight classification

- Macrosomia: Birth weight  $\geq 4$  Kg
- Normal birth weight: 2.500-3.999 Kg
- Low birth weight:  $< 2.500$  Kg

Moderately LBW (MLBW) = 1.500-2.499

Very LBW (VLBW) = 1.000-1.499

Extremely LBW (ELBW)  $< 1.000$

### C) Appropriateness of the weight to gestational age

- AGA: 10<sup>th</sup> - 90<sup>th</sup> %
- SGA  $< 10^{\text{th}}$  % for age
- LGA  $> 90^{\text{th}}$  % for age

#### Causes of LBW

1. Premature neonates
2. Term & post-term (SGA)

Late Preterm: 34-38 wks

## Definition

Preterm baby is any neonate born before 37 weeks ( $< 259$  days)

## Incidence

- 9 %
- 75 % of neonatal mortality

## Etiology of Prematurity

### A) Fetal Causes

- Fetal distress
- Polyhydramnios
- PROM
- Multiple pregnancies
- Hydrops (immune & nonimmune)

### B) Maternal

- ☒ Complications of pregnancy: PIH, antepartum hemorrhage (2)
- ☒ Uterine causes: Incompetent cervix, bicornuate uterus, septate uterus & fibroid
- ☒ Placental causes: Placental insufficiency
- ☒ Maternal diseases
  - HTN & DM
  - Renal & cardiac disease (GN, UTI, CHD...)
  - Anemia & malnutrition
  - Infections: GBS, Listeria...
- ☒ Stress, fatigue & heavy work

### C) Iatrogenic (*Wrong calculation*)

### D) Idiopathic

## Prevention of prematurity

- Antenatal care for early diagnosis & Rx of causes of prematurity (PIH, PN, DM...)
- Avoid stress, heavy work
- Rest & proper diet
- Tocolytics (Ritodrine...) & Cerclage operation



## Problems of Prematurity (All are related to difficulty in extra-uterine adaptation)

System	Immediate	Late
CNS	Hypoxic Ischemic Encephalopathy (HIE) Intracranial hemorrhage (ICH) Seizures Kernicterus Hypotonia	Mental retardation CP (Spastic, choreoathetotic), seizures Learning disabilities Speech & language disorders Microcephaly Hydrocephalus
Hearing & Vision	Retinopathy of prematurity	Hearing & visual impairment Myopia & squint
Respiratory system	Respiratory Failure (RDS) Apnea Pneumothorax	BPD Cor pulmonale Subglottic stenosis Iatrogenic cleft palate
Cardiac	Heart failure PDA (70% if < 1.000 gm)	HTN (Dexamethasone, renal a. stenosis)
GIT	NEC Weak suckling & swallowing	Short bowel syndrome Malabsorption, Malnutrition GERD
Hepatic	Neonatal cholestasis (sepsis, TPN...) Indirect hyperbilirubinemia	Cirrhosis Liver cell failure
Renal	ARF (causes) ↓↓ Na, ↑↑ Na, ↑↑ K, RTA, glucosuria	Nephrocalcinosis HTN (renal artery stenosis)
Nutritional	Nutritional deficiencies	Osteopenia, fracture & deformities FTT
Social	Social stress	Child abuse Divorce
Skin	Injury	Scars (PDA, chest tube), Hernia
Infection	Infection	Recurrent infection (pneumonia)
Hematologic	Anemia, Bleeding (↓↓ PLT, DIC, ↓↓ vit.K)	Bleeding sequelae
Metabolic	↓↓ Ca, ↓↓ Glucose Hypo& Hyperthermia	
Anomalies	↑↑ Frequency of congenital anomalies	3-7 % of LBW

### Prognosis

1. Survival: 95% (1.5-2.5 Kg),
2. Long-term problems (table)
3. Neurologic & Developmental disabilities (table): CP, MR...  
30-50% of VLBW have poor school performance

### Discharge & Follow-up

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> Weight = 1.800-2.100 Kg   | <input checked="" type="checkbox"/> Completion of metabolic screening                    |
| <input checked="" type="checkbox"/> Steady wt increment (10-30 g/day)                               | <input checked="" type="checkbox"/> Eye examination (ROP), When? Who?                    |
| <input checked="" type="checkbox"/> Stable vital signs in open cot ≥ 12 hr                          | <input checked="" type="checkbox"/> Hearing screening                                    |
| <input checked="" type="checkbox"/> Oral intake (nipple, bottle or Ryle)                            | <input checked="" type="checkbox"/> Vaccination (No live attenuated vaccines)            |
| <input checked="" type="checkbox"/> No TPN  | <input checked="" type="checkbox"/> Maternal competence in neonatal care                 |
| <input checked="" type="checkbox"/> No recent apnea or bradycardia                                  | <input checked="" type="checkbox"/> No social risk (teen mother, history of child abuse) |
| <input checked="" type="checkbox"/> No O <sub>2</sub> (some are discharged on home O <sub>2</sub> ) | <input checked="" type="checkbox"/> F/U arrangement                                      |

## Management of Premature Infant

### A) Antenatal Management

- Prevention of prematurity
- Delivery in an equipped hospital

### B) Resuscitation & Stabilization

### C) Nursery Care (*See before*)

### D) Neonatal Care

#### 1. Incubator Care

##### Value:

- Isolation: ↓↓ Risk of infection
- Temperature control (31-32°C) to maintain body temperature at 36.5-37°C
- Humidity (40-60%) to ↓↓ heat loss & to ↓↓ insensible water loss (from the lungs)
- Controlled oxygen supply [Injury from both hypoxia & hyperoxia should be balanced]
- Observation

Estimated heat loss in neonates is 4 times that of an adult  
Preterm NB is at a greater risk

Alternative to incubators: Radiant warmer, heating lamps, room temperature control

#### 2. Hyperbilirubinemia

- Careful monitoring
- Prophylactic phototherapy

#### 3. PDA

- Adequate oxygenation
- Fluid restriction
- Indomethacin (or ibuprofen)
- Surgical ligation

#### 4. Infection

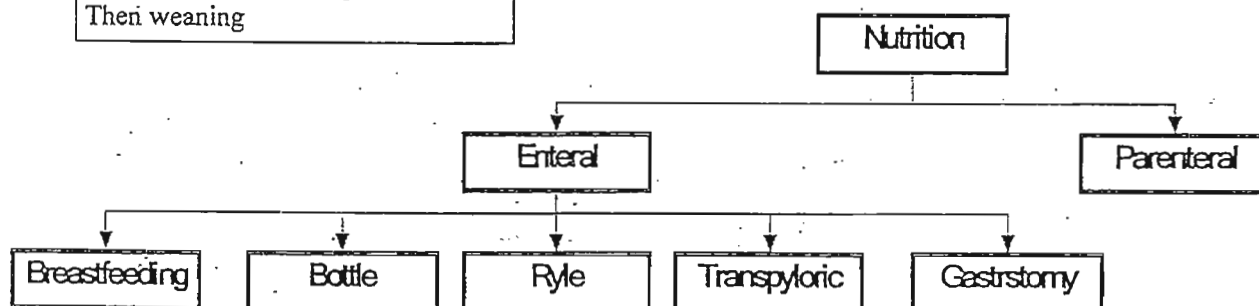
- Strict antiseptic precautions
- Prophylactic antibiotics
- Vaccination (*given according to the chronologic age Not the post-conceptual age*)

#### 5. Fluid & Electrolyte therapy

#### 6. Nutrition

## Feeding of the Premature Infant

Feeding of the term infant  
Exclusive breastfeeding for 6 months  
Then weaning



## Nutritional Requirements

Item	Requirements	Comments
Energy	120-140 Kcal/Kg/day Max = 180 Kcal/Kg/day [Maintenance of BW = 50 Weight Gain = 70-90]	<ul style="list-style-type: none"> <li>▪ <math>\uparrow\uparrow</math> Energy intake &gt; 180 is <u>Not</u> utilized for growth</li> <li>▪ <math>\uparrow\uparrow</math> Energy <math>\rightarrow</math> <math>\uparrow\uparrow</math> <math>\text{NH}_3</math>, BUN, Na &amp; Acidosis</li> <li>▪ <math>\uparrow\uparrow</math> Energy requirements in HF, RDS, BPD &amp; SGA</li> </ul>
Proteins	3.5 g/Kg/day	<ul style="list-style-type: none"> <li>▪ Breast milk is inadequate for preterm &amp; LBW</li> <li>▪ <math>\uparrow\uparrow</math> Protein intake &gt; 4-5 gm/Kg/d <math>\rightarrow</math> <math>\uparrow\uparrow</math> <math>\text{NH}_3</math>, BUN, Na &amp; Acidosis</li> </ul>
CHO	11-16 g/Kg/day	
Fat	5-7 g/Kg/day	<ul style="list-style-type: none"> <li>▪ Should constitute 40-50% of calories</li> <li>▪ <math>\uparrow\uparrow</math> Fat intake <math>\rightarrow</math> Ketosis</li> </ul>
Water	Term = 150 cc/kg/day VLBW $\geq$ 200 cc/kg/day	<p><math>\downarrow\downarrow</math> Water intake with <math>\uparrow\uparrow</math> Calories in:</p> <ul style="list-style-type: none"> <li>▪ HF, RDS &amp; BPD</li> <li>▪ PDA</li> </ul> <p><math>\uparrow\uparrow</math> Requirements in:</p> <ul style="list-style-type: none"> <li>▪ Phototherapy</li> <li>▪ Radiant warmer</li> <li>▪ <math>\downarrow\downarrow</math> Humidity</li> </ul>
Ca	100-200 mg/Kg/day	▪ Breast milk is inadequate
P	60-120 mg/Kg/day	▪ Ca supplementation is required
Na	3-5 mEq/Kg/day	▪ Breast milk is inadequate + $\uparrow\uparrow$ Renal loss
K	2-3 mEq/Kg/day	▪ $\uparrow\uparrow$ Renal loss
Iron	2-4 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Iron stores are adequate in term NB for 2 months</li> <li>▪ Preterm require iron supplementation once they are on full enteral feeds</li> <li>▪ 2-4 mg/Kg/day (for 6-12 months)</li> <li>▪ For Rx: 6 mg/Kg/day</li> <li>▪ Iron is an oxidant agent</li> </ul>
Vitamin A	1,500 IU/Kg/day	▪ $\downarrow\downarrow$ Incidence of BPD
Vitamin D	400-1,000 IU/day	▪ $\downarrow\downarrow$ Incidence of osteopenia of preterm
Vitamin E	6-12 IU/Kg/day	<ul style="list-style-type: none"> <li>▪ Vitamin E is an anti-oxidant <math>\rightarrow</math> protection of PUFA in RBC membrane</li> <li>▪ <math>\downarrow\downarrow</math> Vitamin E + Iron therapy <math>\rightarrow</math> Syndrome of (Hemolytic anemia + Edema + Thrombocytosis)</li> <li>▪ Vitamin E <math>\rightarrow</math> <math>\downarrow\downarrow</math> PNL function <math>\rightarrow</math> <math>\uparrow\uparrow</math> Susceptibility to sepsis</li> <li>▪ Vitamin E <math>\rightarrow</math> Hyperosmolar preparation <math>\rightarrow</math> <math>\uparrow\uparrow</math> Susceptibility to NEC</li> </ul>
Vitamin K		▪ Given routinely to all NB for # HDN (0.5-1 mg IM)
Vitamin C		Multivitamin supplementation
Vitamin B		
Folic		
Trace Elements	Zn, Cu, Mn, Selenium, Chromium, Iodine	Present in adequate amount in preterm formulas

## Enteral Feeding

Feeding of the preterm infant should be **individualized**

### Type of milk

1. Breast milk is recommended for preterm but needs fortification [human milk + Fortifier]  
Without fortification, breast milk is not suitable for preterm
2. Low-birth weight formula

Sign	Energy	Protein	Fat	CHO	Na	K	Ca	PO <sub>4</sub>
Breast Milk	67 Cal %	1.25 g %	3.9 g %	7 g %	7	15	28	14
LBW formula	81 Cal %	2.2 g %	3.9 g %	8.5 g %	13-20	18	80	40

### Supplementation is required:

- Vitamins (A, D, E, C, B, Folic)
- Iron (2-4 mg/Kg/day) for 6-12 months

### Routes of Enteral Feeding

1. Oral (Breast & Bottle)
2. Gastric feeding (Nasogastric & orogastric enteral feeding)
3. Transpyloric feeding
4. Gastrostomy feeding

### Value of Early Enteral Feeding

1. ↓↓ Risk of dehydration
2. ↓↓ Risk of hypoglycemia
3. ↓↓ Risk of hyperbilirubinemia

Glucose 5% should be used in the 1<sup>st</sup> oral feed (to exclude TOF)

### A) Oral Feeding

#### Methods of oral feeding

##### a. Breastfeeding

It may be allowed for premature NB  $\geq 34$  wks gestation (Coordinated reflexes)

##### b. Bottle Feeding

Using expressed breast milk or LBW formula in premature NB  $\geq 34$  wks

Suck-Swallow-breath reflexes

#### Precautions of oral feeding

1. Gestational age  $\geq 34$  weeks (coordinated suck-swallow-breath reflexes)
2. Respiratory rate  $< 60$ /minute
3. Absence of contraindications

#### Contraindications of oral feeding (= Indications...)

1. Immaturity
  - a. Preterm  $< 34$  weeks (Weak suckling & swallowing)
  - b. LBW  $< 1.500$  gm (Energy loss!!)
2. CNS depression
3. Perinatal asphyxia & Hypoxia
4. Respiratory distress
5. Circulatory failure (shock, hypotension, hypothermia, poor perfusion)
6. Sepsis
7. Suspected structural anomalies (TOF, IO...)
8. Feeding intolerance

Small soft nipples with large holes, Why?

## B) Gavage Feeding


**Definition:** Nasogastric or orogastric enteral feeding

### Indication:

- Preterm < 34 weeks (Weak suckling & swallowing)
- LBW < 1.500 gm
- Contraindications of oral feeding (Except...)

### Technique:

Soft plastic tube 5 French (rounded tip with 2 side holes)

The location of the tube must be checked before every meal 

The measured amount is allowed to flow slowly (by gravity)/3-4 hr

The tube can be introduced before each feed or changed every 2-3 days

- |  |
|--|
| <ol style="list-style-type: none"> <li>1. aspiration</li> <li>2. Air bubbles</li> <li>3. Cyanosis</li> </ol> |
|--|

### Routes:

#### a. Nasogastric:

- ↑↑ Airway resistance
- ↑↑ Respiratory rate (obligate nasal breathers)
- ↑↑ Risk of otitis media
- Injury of the nasal septum
- Better fixation

#### b. Orogastric

### Methods:

- a. Intermittent (bolus)
- b. Continuous: at a slow rate (CHPS, GERD, RDS...)

## C) Transpyloric feeding

### Technique:

Soft plastic tube is advanced beyond the pylorus into the distal duodenum or jejunum

### Indication:

- Gastric retention
- GERD
- To ↓↓ risk of aspiration

### Disadvantages

- Bacterial overgrowth
- Malabsorption
- Dumping effect & diarrhea (↑↑ intestinal osmolarity)
- Intestinal perforation

## D) Gastrostomy Feeding

### Indication:

- TOF
- Chest surgery

## Signs of Feeding Intolerance

1. Bilious (greenish) or bloody (brownish) gastric residue
2. ↑↑ Residue (>25% of the previous feed)
3. ↑↑ Abdominal girth
4. Vomiting
5. Bloody stools (+ve heme test)
6. Watery stools (+ve reducing substances)

## Contraindications of Enteral Feeding (Absolute)

- NEC
- Intestinal surgery
- Severe prematurity

Gut integrity is dependent  
on enteral nutrition

## **Trophic Feeding** (Gut priming or early enteral feeding)

**Definition:** Small amounts of enteral feeding in neonates not tolerating regular feed

**Type of milk:** Expressed breast milk or 1/2 or full strength LBW formula

**Onset:** ASAP after birth ideally on D<sub>2</sub>

**Volume:** Start with 1 cc/6 hrs & advance slowly to 10-20 cc/Kg/day

### **Advantages:**

- ↑↑ GIT motility
- ↑↑ GIT maturity
- ↑↑ GIT hormones
- ↓↓ Serum bilirubin
- ↓↓ Time needed to establish full enteral feeding
- ↓↓ Time on TPN

### **Indications:**

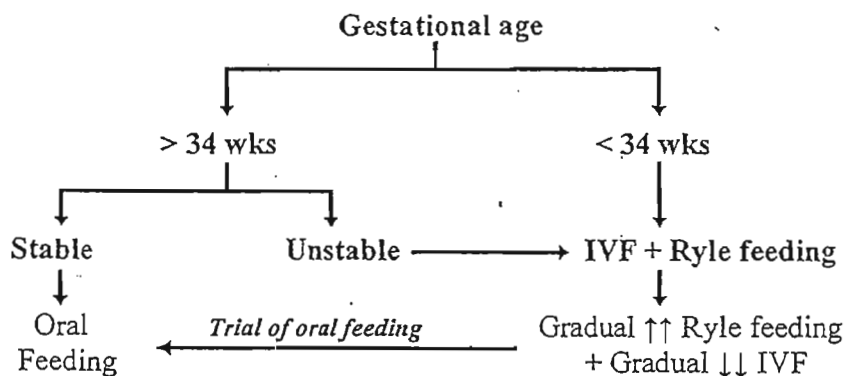
- Gut priming specially in ELBW
- Term NB with mild instability
- Umbilical artery catheter (↑↑ Risk of NEC)

### **Contraindications:**

- NEC
- Intestinal surgery

## **Special considerations of Enteral Feeding**

- Gut integrity is dependent on enteral nutrition, so **careful early** feeding is recommended
- Trophic feeding can be started **even** in ELBW
- Initial feeds are EBM, 1/2 or full strength
- Start with small volumes then ↑↑ gradually guided by the available protocols & tolerance
- The daily volume increments should not exceed 10-20 cc/Kg/day
- Aim = 150 cc/Kg/day = 120 Kcal/Kg/day
- The remaining part of the total fluid requirements is given as parenteral nutrition (TPN or IV fluids)



## **Assessment of Nutrition & Growth**

### **A) Clinical**

- Weight (*daily*)
- Length (*weekly*)
- Head circumference (*weekly*)

### **B) Laboratory**

- Serum albumin, Ca, PO<sub>4</sub>, ALP, Hb

## Parenteral Feeding

### A) Intravenous Fluids (Partial parenteral nutrition)

Indications: (Almost all preterm NB require IVF)

- ☑ Transient till establishment of adequate enteral feeding (preterm, sick term NB...)
- ☑ Contraindications of enteral nutrition (NEC, intestinal surgery...). If enteral intake is not expected for > 3 days, TPN should be used

### Fluid Requirements (cc/Kg/day)

	C%	Day 1	Day 2	Day 3	Day 4 & over
≥ 2.500 gm	10%	60-80	90	100	↑↑ by 10 cc/Kg/day till 150 cc/Kg/day
1.500-2.500 gm	10%	80	100	110	↑↑ by 10 cc/Kg/day till 150-180 cc/Kg/day
1.000-1.500 gm	7.5%	100	120	130	
< 1.000 gm	5%	120	140	170	

- Subtract 20 cc/Kg/day in case of RD
- Add 20 cc/Kg/day in case of phototherapy, radiant warmer or fever

### Electrolyte Requirements

	Day 1	Day 2	Day 3
Na	-	2-3 mEq/Kg/day	2-3 mEq/Kg/day
K	-	1-2 mEq/Kg/day	1-2 mEq/Kg/day
Ca	35 mg/Kg/day	35 mg/Kg/day	35 mg/Kg/day

- Do not add Na if serum Na > 140 mEq/L
- Do not add K if serum K > 4.5 mEq/L
- Do not add K until urine output is established
- Use Glucose 5-10%

3 mEq/Kg/day = NS 20 cc/Kg/day  
This volume is subtracted from total IVF

Ca: 35 mg/Kg/day = 4 cc/Kg/day

### Assessment of hydration status of NB

#### A) Clinical

- Weight
- Skin
- Fontanel
- Urine volume

#### B) Laboratory

- Serum Na
- Urine: Specific gravity & Glycosuria

### Example

Calculate the IVF of a preterm neonate 2 Kg

Day 1: Total volume = 160 cc

Type of fluids = 150 cc Glucose 10% + 8 cc Ca gluconate

Day 2: Total volume = 200 cc

Type of fluids = 150 cc Glucose 10% + 8 cc Ca gluconate + 40 cc NS + 1 cc KCl

Day 3: Total volume = 220 cc

Type of fluids = 170 cc Glucose 10% + 8 cc Ca gluconate + 40 cc NS + 1 cc KCl

Day 4: Total volume = 240 cc

Type of fluids = 190 cc Glucose 10% + 8 cc Ca gluconate + 40 cc NS + 1 cc KCl

Day 5: Total volume = 260 cc

Type of fluids = 210 cc Glucose 10% + 8 cc Ca gluconate + 40 cc NS + 1 cc KCl

Any enteral feeds should be subtracted from the total volume

## B) Total Parenteral Nutrition (TPN)

### Definition:

IV delivery of energy & nutrients

### Indications:

- ☑ Short term indications ( $\approx$  1 month)
  - Prematurity if full enteral intake is not expected within 3-7 days
  - Congenital GIT anomalies (TOF, IO, gastroschisis, diaphragmatic hernia)
  - NEC
- ☑ Long term indications
  - Malabsorption syndromes: Congenital microvillous atrophy, Tufting enteropathy...
  - Short bowel syndrome
  - Inflammatory bowel syndrome

### Vascular Access

1. Peripheral veins
  - Only iso-osmolar solution can be used (Glucose % should not exceed 12.5%)
  - It is the route of choice for intralipids
2. Central veins
  - Surgically inserted (Subclavian or internal jugular vein)
  - PICC (peripherally inserted central catheters) into SVC or IVC
3. AV fistula (in long term indications)

### Solutions of TPN

1. Glucose: [1 gm = 3.4 Kcal]
2. Amino acids: [1 gm = 3.4 Kcal]
3. Intralipids: [1 gm = 10 Kcal]
4. Electrolytes (Na, K, Ca, PO<sub>4</sub>, Mg, Mn, Cu, Fe, Se)
5. Vitamins (fat-soluble & water-soluble)

### Requirements

	Initial dose	Subsequent adjustment
Fluid	60-80 cc/Kg/day	↑↑ by 10 cc/Kg/day till 150 cc/Kg/day
Energy	Term = 120 Kcal/Kg/day	Preterm = 120-140 Kcal/Kg/day
Glucose	6-8 mg/Kg/min	↑↑ the rate up to 10-14 mg/Kg/min
Proteins	0.5-1 gm/Kg/day	↑↑ by 0.5 up to 2.5-3 gm/Kg/day
Lipids	0.5-1 gm/Kg/day	↑↑ by 0.5 up to 2.5-3 gm/Kg/day
Electrolytes	Added according to the daily requirements	
Vitamins	[Na = 2-3 mEq/Kg/day, K = 1-2 mEq/Kg/day, Ca = 35 mg/Kg/day ...]	

### Complications

#### A) VA-related complications

- Insertion: arterial injury, pneumothorax & hemothorax
- Infection (local & systemic)
- Thrombosis
- Dislodgement
- Bleeding (Heparin)



## B) Metabolite-related complications

### 1. Glucose metabolism

- Hyperglycemia
- Glycosuria → Osmotic diuresis → Dehydration

### 2. Protein metabolism

- Hyperammonemia (encephalopathy)
- Hypermethioninemia
- Metabolic acidosis

### 3. Lipid metabolism

- Hyperlipidemia
- ↓↓ Essential FA (Linoleic, Linolenic...)
- Sepsis (↓↓ PNL phagocytic activity)
- Bleeding (Platelet dysfunction = Adhesion defect)
- Hypoxia (↓↓ O<sub>2</sub> diffusion)
- Cholestasis, fatty liver, GB stones

### 4. Electrolyte disturbances

### 5. Metabolic bone disease (Ca & PO<sub>4</sub> disturbances)

Cause: Ca & PO<sub>4</sub> disturbances

C/P: Rickets-like

Lab: ↑↑ ALP

X-rays: Rickets

### 6. Vitamin deficiency

### 7. GIT: (Appear when enteral feeding is resumed)

- ↓↓ GIT motility
- ↓↓ GIT secretion (gastric, pancreatic & intestinal)
- ↓↓ Enzymatic activity (Brush border)

## Cholestasis associated with TPN

### Risk factors

- Prematurity (15% in preterm < 32 wks)
- Duration (usually > 2 wks)
- Lack of enteral intake (No bile flow) →
- Ileal resection (↓↓ Enterohepatic circulation)

### Pathogenesis

1. Concomitant condition: infection, hypoxia, drugs...
2. Fasting (↑↑ Risk of cholestasis)
3. Amino acids in TPN
  - Methionine (↓↓ Bile flow)
  - Tryptophan (Photodegradation products of tryptophan are hepatotoxic)
4. ↓↓ Essential FA & Carnitine
5. ↓↓ Taurine (↓↓ Bile salt synthesis)
6. Formation of biliary sludge

### Clinical Picture

Jaundice ± HSM

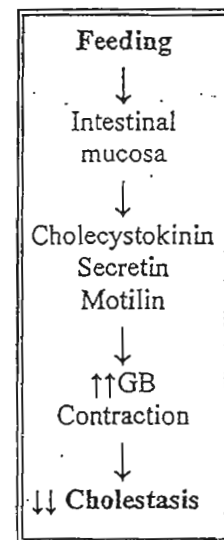
### Investigations

Conjugated hyperbilirubinemia, ↑↑ ALT, AST & GGT

### Treatment

Rx of risk factors

↑↑ Enteral feeding



Protection from light

### Side Effects of Drugs given to Preterm Infants

	Drug	Effect
1	Aminoglycosides	Nephrotoxicity, Ototoxicity
2	Amphotericin B	Nephrotoxicity, DI
3	Chloramphenicol	Grey baby syndrome
4	Tetracycline	Enamel hypoplasia, pigmentation of teeth
5	Sulfonamide	Hyperbilirubinemia, hemolysis in G6PD deficiency
6	Vitamin K	Hyperbilirubinemia
7	ACE inhibitors (Captopril)	Renal impairment, oliguria
8	Indomethacin	Renal impairment, oliguria, bleeding, perforation
9	Oxygen	ROP, BPD
10	Prostaglandins	Apnea, Bradycardia
11	Dexamethasone	HTN, GIT bleeding, Hyperglycemia
12	Furosemide	Ototoxicity, Nephrocalcinosis
13	Tolazoline	Hypotension
14	NaHCO <sub>3</sub>	IVH
15	Phenobarbitone	Drowsiness
16	Heparin	Bleeding
17	Calcium	SC necrosis
18	Iodine antiseptics	Neonatal goiter, Hypothyroidism
19	Erythromycin	Pyloric stenosis

## Large for Gestational Age (LGA)

### Definition

Infant weight > 90<sup>th</sup> % for age (2 SD above the mean for gestational age) or ≥ 4.000 gm

### Etiology

1. IDM
2. Constitutional
3. Some post-term infants
4. Hydrops
5. Beckwith-Wiedemann syndrome

### Complications

- |                 |                         |
|-----------------|-------------------------|
| 1. Birth injury | 3. Hypoglycemia         |
| 2. Polycythemia | 4. Congenital anomalies |

### Management

#### A) Antepartum Management

- Antenatal care for early diagnosis & Rx of DM & hydrops and for assessment of G.Age
- Delivery in an equipped hospital

#### B) Intrapartum Management

- Resuscitation & Stabilization
- Careful delivery to avoid birth injury

#### C) Postpartum Management

- Nursery care (as before)
- Diagnosis & Rx of potential complications...

# Intrauterine Growth Retardation (IUGR)

## (SGA)

### Definition

Infant weight < 10<sup>th</sup> % for age (2 SD below the mean for gestational age)

### Types

	Symmetric IUGR	Asymmetric IUGR
Pattern	Continuous low profile pattern	Late flattening pattern
Onset of IUGR	Early in pregnancy	Late (3 <sup>rd</sup> trimester)
Features	Length, wt & skull circumference are equally affected	Head is spared (relatively large)
Causes	<ul style="list-style-type: none"> <li>▪ Chromosomal disorders</li> <li>▪ Congenital infection (TORCH)</li> <li>▪ Congenital anomalies</li> <li>▪ Radiation</li> <li>▪ Severe placental insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>▪ Placental insufficiency (<i>mention</i>)</li> <li>▪ Maternal causes of IU asphyxia (??)</li> <li>▪ Maternal malnutrition</li> <li>▪ Multiple pregnancies</li> </ul>
Perinatal asphyxia	Usually absent	Usually present.
Low Apgar score		
N. Hypoglycemia		

### Complications

- |  |   |
|--|---|
| <ol style="list-style-type: none"> <li>1. IU fetal hypoxia (fetal distress)</li> <li>2. Perinatal asphyxia</li> <li>3. PPHN</li> <li>4. MAS</li> </ol> | <ol style="list-style-type: none"> <li>5. Polycythemia</li> <li>6. Hypothermia (↓↓ Energy, ↓↓ SC)</li> <li>7. Hypoglycemia &amp; Hypocalcemia</li> <li>8. Congenital infection, anomalies, chromosomal</li> </ol> |
|--|---|

### Management

#### A) Antepartum Management

- Antenatal care for early diagnosis & Rx of causes of placental insufficiency (PIH, HTN...)
- Proper assessment of gestational age
- Antepartum assessment of fetal well being (= Diagnosis of placental insufficiency??)
- Assessment of fetal functional maturity (lung maturity, how?)
- Early delivery (if the risk of IU hypoxia is > risk of prematurity)
- Steroids for prevention of RDS
- Delivery in an equipped hospital

#### B) Intrapartum Management

- Intrapartum assessment of fetal well being??
- Resuscitation & Stabilization
- Proper management of expected complications (MAS, perinatal asphyxia...)

#### C) Postpartum Management

- Nursery care (*as before*)
- Early feeding is important (↓↓ Glucose)
- Diagnosis & Rx of potential complications...

### Prognosis

- Depends on the etiology
- Lower risk of neonatal mortality than preterm infants with the same weight
- Potential complications...

# Post-Term Infants

## Definition

Post-term baby is any neonate born  $\geq 42$  weeks ( $\geq 294$  days)

Post-mature baby is any neonate born  $\geq 41$  weeks ( $\geq 287$  days)

Postmaturity syndrome = Post-term + Placental insufficiency

## Etiology (Unknown\*)

1. Miscalculation
2. Associations: anencephaly, trisomies (18, 16), multigravidity, IDM

## Clinical Picture

### A) Placental insufficiency

- Skin: pale, dry, wrinkled, absent lanugo hair & vernix caseosa with loss of SC fat
- Hair: abundant scalp hair
- Nails: long
- Meconium staining  $\pm$  MAS
- Unusual degree of alertness
- Complications: MAS, PPHN, perinatal asphyxia, HIE, polycythemia,  $\downarrow\downarrow$  Ca,  $\downarrow\downarrow$  Glucose

### B) No placental insufficiency

- $\uparrow\uparrow$  Birth weight, head (well ossified & less moldable)
- $\uparrow\uparrow$  Incidence of dystocia

## Management

### A) Antepartum Management

- Antenatal care
- Proper assessment of gestational age
- Antepartum assessment of fetal well being (= Diagnosis of placental insufficiency??)
- Delivery in an equipped hospital

### B) Intrapartum Management

- Resuscitation & Stabilization
- Intrapartum assessment of fetal well being

### C) Postpartum Management

- Nursery care (*as before*)
- Early feeding is important ( $\downarrow\downarrow$  Glucose)
- Diagnosis & Rx of potential complications...

## Prognosis

- Higher risk of neonatal mortality than term infants with the same weight
- Potential complications...

## Multiple Pregnancies

### Incidence

- Twins = 1: 86      Triplets = 1: 86<sup>2</sup>      Quadruplets = 1: 86<sup>3</sup>
- 1/3 of twins are monozygotic (MZ) = Uniovular = Identical
- 2/3 of twins are dizygotic (DZ) = Binovular = Non-identical
- The incidence of MZT is relatively constant
- The incidence of DZT is affected by:
  - Maternal age & parity (↑↑)
  - Use of reproductive technology (clomiphene, In vitro fertilization)

Chorion is formed around D<sub>3</sub>  
Amnion is formed around D<sub>8</sub>

### Etiology

- ☒ Monozygotic twins: develop from splitting of a single zygote (single fertilized ovum)

Splitting	Freq.	Placenta	Chorion	Amnion	Cords	Term
1 <sup>st</sup> 3 days	25	2	2	2	2	Dichorionic-diamniotic
Days 4-8*	75	1	1	2	2	Monochorionic-diamniotic
Days 9-15	-	1	1	1	2	Monorionic-monoamniotic
> D 15	-	1	1	1	2	Conjoined twins

Conjoined twins (Craniopagus, thoracopagus...)

- ☒ Dizygotic twins: develop from 2 fertilized ova [2 ova + 2 sperms]  
Always Dichorionic-Diamniotic

### Genetic Consideration

- MZT have the same genotype (one fertilized ovum)
- DZT have different genotypes (two fertilized ova)

### Diagnosis of Zygosity (depends on sex, placenta, blood group & HLA typing)

Type	MZT	DZT
Etiology	Splitting of a single zygote (One ovum)	Develop from 2 fertilized ova
Placenta & Fetal membrane	<ul style="list-style-type: none"> <li>▪ 75% are (Monochorionic-diamniotic): [1 Placenta + 1 Chorion + 2 Amnions]</li> <li>▪ 25% are (Dichorionic-diamniotic): [2 Placentas + 2 Chorions + 2 Amnions]</li> </ul>	Always Dichorionic-diamniotic [2 Placentas + 2 Chorions + 2 Amnions]
Markers	Sex	The same
	Hair	May be different
	Eye	"
	Blood group	"
	HLA group	"
Skin grafts	Well accepted	Rejected if different HLA
Dermatoglyphics	Homolateral hands are more similar than both hands of the same co-twin	Homolateral hands are less similar than both hands of the same co-twin

### IU growth

- Till 29 wks of gestation → The same weight as singleton (of the same GA)
- After 33 wks of gestation → The weight of each twin is less than the singleton
- Average weight at term = 2.600 gm [average singleton = 3.200 gm]

### Diagnosis of Multiple Pregnancies

- a. Examination: Fundal level
- b. Imaging: U/S

## Complications

### A) Maternal

- Abortion
- Hyperemesis gravidarum
- PIH
- Polyhydramnios
- PROM
- Pressure symptoms

### B) Fetal

- Prematurity
- IUGR
- Abnormal presentation
- Congenital anomalies (more with MZT), Why?
- Asphyxia

### C) 2<sup>nd</sup> Twin (↑↑ Mortality)

- Retained 2<sup>nd</sup> twin
- ↑↑ asphyxia, ↑↑ anesthesia, ↑↑ RDS

#### Diagnosis of TTTS:

1. Hb difference  $\geq 5$  gm%
2. Wt difference  $\geq 20\%$

### D) Placental vascular shunts

They occur in almost all monochorionic twins & almost never in dichorionic twins

- Artery to artery } *Usually with No complications*
- Vein to vein }
- Artery to vein: may cause "twin to twin transfusion syndrome"

	Donor	Recipient
Weight	Small	Large
Nutrition	Malnourished	Well nourished
Glomeruli	Small	Large
Amniotic fluid	Oligohydramnios	Polyhydramnios
Hb	Anemia (pallor)	Polycythemia (plethora)
Blood Volume	Hypovolemia	Hypervolemia
Heart size	Microcardia	Cardiac hypertrophy
Heart failure	Heart failure (anemia)	Heart failure (hypervolemia)
Hydrops	Hydrops	
Gestational Age	Prematurity	

## Management

### A) Antepartum Management

- Antenatal care including U/S
- Proper assessment of gestational age
- Delivery in an equipped hospital

### B) Intrapartum Management

- Two teams should be present (Complications is more in the 2<sup>nd</sup> twin)
- Resuscitation & Stabilization

### C) Postpartum Management

- Nursery care (*as before*)
- Determination of zygosity & family support
- Diagnosis & Rx of potential complications...

Donor: Anemia (packed RBC)

Recipient: Neonatal jaundice (phototherapy  $\pm$  exchange transfusion)

Heart failure (Anti-failure)

# Neonatal Resuscitation

Ventilation is the key  
Chest compression &  
drugs are rarely needed

## Definition

It is a rapid sequence of steps to be initiated if there is impairment of respiration or circulation of the newborn infant. 5-10% of newborns require some degree of resuscitation

## Goals

- A) Airway: Suction of the upper airways ± ETT  
Positioning: head in the midline & slightly extended
- B) Breathing: Tactile stimulation  
Supplementary O<sub>2</sub>  
Positive pressure ventilation (bag & mask or ETT)
- C) Circulation: Chest compression & Drugs

All through, do not allow  
the newborn to get cold.

### Hypothermia:

- Acidosis
- Hypoglycemia

## Equipments & Preparation

- Radiant warmer & warm towels
- Suction & suction catheters
- O<sub>2</sub> source (flowmeter) & O<sub>2</sub> tubing
- Face masks (?size) & Ambu-bag
- ETT (2.5, 3, 3.5, 4 mm)
- Laryngoscopes (0 & 1) & check light
- Syringes (1, 3, 5, 10, 50 ml)
- Umbilical catheters (5 F)
- Stethoscope
- Drugs: adrenaline, NaHCO<sub>3</sub>, Ca, naloxone
- Transport incubator

## Resuscitation Technique

1. Review obstetric records
2. Proper hand washing
3. Check equipments & preparation
4. Ask 5 question??
5. Keep the neonate dry, warm & in good position
6. Suction of the upper airways; mouth, nose & oropharynx (avoid vigorous suction)
7. Gentle tactile stimulation may be needed (rubbing of the back + slapping of the soles)
8. Assessment of Apgar score (*discuss*)

## Sequence of intervention

- A) No asphyxia (Apgar = 8-10): as before
- B) Mild asphyxia (Apgar = 5-7): [Spontaneous breathing & HR > 100/min]  
 → Tactile stimulation + supplementary O<sub>2</sub>
- C) Moderate asphyxia (Apgar = 3-4): [Apnea & HR < 100/min]  
 → Positive pressure ventilation (Bag & mask) at a rate of 40-60/min (20 cm H<sub>2</sub>O pressure)  
 → Reevaluation (30 sec):
- a. HR > 100/min, spontaneous breathing & pink → Ongoing care
  - b. Apnea & HR > 60/min → Continue PPV & Reevaluate (30 sec)
  - c. Apnea & HR < 60/min → Consider ETT & Chest compression

### Ongoing care (NICU)

- Physical examination
- CXR

Chest compression (using both thumbs; other fingers support the back) at a rate of 120/min

Compression: Ventilation ratio = 3:1

Adequacy of compression is determined by palpating the femoral pulse

Reevaluation after 30 sec of combined ventilation & chest compression

- a. HR > 60/min → Stop compression & continue ventilation
- b. HR < 60/min → Drugs

- D) Severe asphyxia (Apgar = 0-2): [at any time]

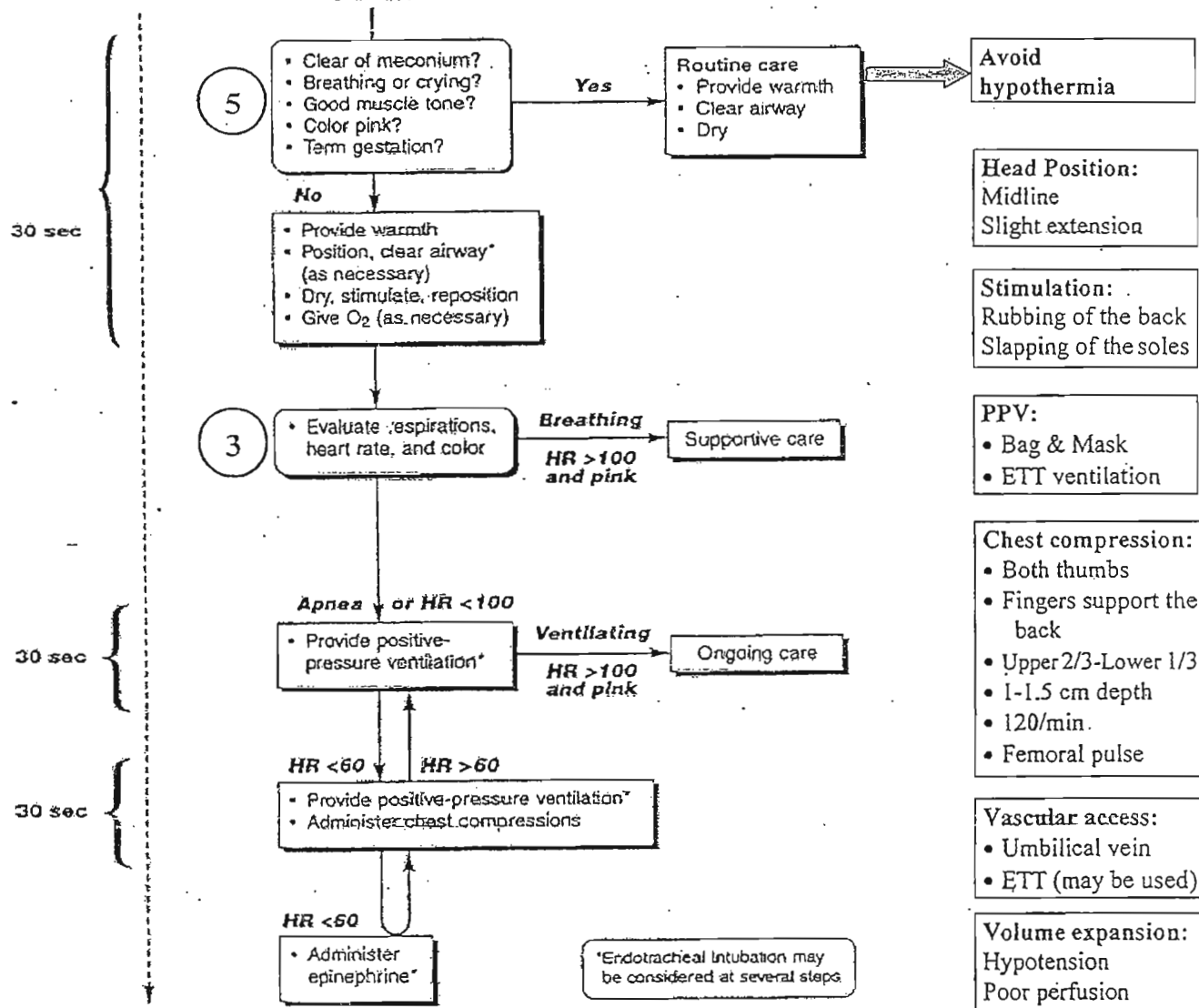
Initial stabilization (dry, warm, position), suction, PPV (bag & mask), ETT, chest compression & drugs (adrenaline, NaHCO<sub>3</sub>, volume expander, naloxone)

## Algorithm

Be calm!!

Approximate time

### Birth



Algorithm for resuscitation of the newly born infant.

### Drugs for neonatal resuscitation (drugs are not effective unless ventilation is effective)

Drug	Concentration	Dose	Indications
Adrenaline	1:10,000	IV: 0.1-0.3 cc/Kg ET: 0.3-1 cc/Kg	HR < 60/min after combined ventilation & chest compression
Volume expander	NS, Albumin 5% Whole blood	10-20 cc/Kg IV	Hypotension, Hypoperfusion Blood loss
Glucose	10%	2 cc/Kg IV	Hypoglycemia
NaHCO <sub>3</sub>	5% & 8.4%	1-2 mEq/Kg (slowly)	Prolonged arrest
Naloxone	0.4 mg/ml	0.1-0.3 cc/Kg IV or ET	Maternal morphine

### Indications of ETT

1. Airway patency (goiter, micrognathia)
2. Tracheal suction (MAS)
3. Ineffective bag & mask ventilation
4. Drugs & Surfactant therapy
5. Prolonged ventilation needed

Duration of Resuscitation 15-20 minutes

### Causes of low Apgar:

1. Intra-partum asphyxia
2. CNS depression (anesthesia)
3. CNS anomalies
4. Congenital myopathy
5. Congenital neuropathy
6. MgSO<sub>4</sub>
7. Trauma (spinal cord)
8. Hypovolemia



## Infant Transport

### Definition

It is neonatal transfer of high-risk infants delivered at a hospital without advanced services to a tertiary care center (Level III)

### Indications

1. Prematurity (< 32 wks) &/or LBW (< 1.500 gm)
2. RD requiring ventilatory support
3. CHD or cardiac arrhythmias
4. Severe HIE
5. Congenital anomalies
6. Metabolic diseases
7. Surgical emergencies (TOF...)

### Requirements

#### A) Transport personnel

- Team of at least 2 trained individuals (physician & nurse)
- Experience required: IV cannulation, intubation & chest tube placement

B) Medications	C) Supplies	D) Equipments
Adrenaline	Alcohol (Steryllium)	Transport incubator
Atropine	Betadine	Monitors (HR, BP, O <sub>2</sub> %, Temp.)
NaHCO <sub>3</sub>	Gauze & dressings	Suction device
Calcium	Gloves, gowns	Infusion pumps
Dexamethasone	IV Catheters (22, 24 gauge)	Laryngoscopes (Blades 0 & 1)
KCl	Butterfly needles	Magill forceps
	Umbilical catheters (5 F)	Ventilation bag
Albumin 5%	Syringes (1, 3, 5, 10, 50 ml)	Stethoscope
Glucose 10% & 50%	IV tubing	Tanks of O <sub>2</sub> & compressed air
Sterile water	Stopcocks	Source of electrical power
	Suction catheters (6, 8, 10 F)	Mechanical ventilator
Dopamine	Feeding tubes (5, 6, 8 F)	
Dobutamine	ETT (2.5, 3, 3.5, 4 mm)	
Digoxin	Face masks (preterm & term)	
	Airways	
Phenobarbitone	Oxygen tubing	
Phenytoin	Chest tubes (10, 12 F)	
Midazolam	Tape	
	Lubricating gel (K-Y)	
Ampicillin	Scalpel	
Gentamicin	Suture material (silk 3-0, 4-0)	
Erythromycin eye ointment	Thermometer	
PGE <sub>1</sub>	BP cuffs	

#### E) Transport Vehicle: Ambulance or helicopter (if the distance > 100 miles)

It should be large enough to accommodate the team & equipments [Rapidly available]

#### F) Transport process:

- Consent
- Transport after stabilization
- Reassure the mother
- The father should follow the vehicle

#### G) Stabilization (*Before leaving the referring center*)

1. Airways: ETT may be needed
2. Breathing: O<sub>2</sub>, mechanical ventilation, chest tube (if pneumothorax)
3. Circulation: Vascular access (peripheral or umbilical catheter)
4. Temperature
5. Metabolic stabilization: Rx of hypoglycemia
6. Hemodynamic stabilization: Volume expanders for hypotension
7. Initiation of antibiotic therapy (*after taking suitable cultures*)
8. Specific conditions
  - Diaphragmatic hernia: NGT + ETT
  - TOF: Continuous gentle suctioning from the pharyngeal pouch
  - Abdominal wall defects (gastroschisis & exomphalos major...)
  - Neural tube defects (meningomyelocele...)
  - Anemia: packed RBC (non-matched O -ve blood can be given)
  - Hydrops: Anemia + pleural effusion (Chest tube)
  - Congenital cyanotic heart disease (PGE<sub>1</sub> to maintain duct patency)

*Wrapping with warm, sterile, saline soaked gauze*

#### H) Post transport responsibilities

- Complete & accurate information should be given to the hospital team
- Complete documentation of the clinical course & problems surrounding the transport

# Perinatal Asphyxia

## (Hypoxic-Ischemic Encephalopathy)

Anoxia: Complete lack of O<sub>2</sub>  
Hypoxia: Lack of O<sub>2</sub>  
Ischemia: Lack of blood flow

### Definition

Asphyxia is a condition of impaired gas exchange that leads to 3 biochemical effects:

Hypoxia, Hypercapnia & Metabolic acidosis

The term asphyxia should not be used unless all the following criteria are met:

1. Umbilical cord blood pH < 7
2. Apgar score 0-3 for ≥ 5 minutes
3. Neurological manifestations (e.g., Seizures, coma, hypotonia...)
4. Multisystem organ dysfunction

4

HIE is permanent brain damage due to hypoxia &/or ischemia → Death or long-term...

### Incidence

1-1.5%

### Etiology

#### A) Intrauterine causes

##### a. Maternal causes

- Cardiac: Heart failure, Shock
- Respiratory failure
- Severe anemia
- Hypotension (blood loss)
- Eclampsia (convulsions)

##### b. Placenta (Placental insufficiency)

##### c. Cord

- Compression (fetal head, forceps)
- Prolapse
- Ruptured vasa previa

##### d. Compression of fetal head

- Pelvis (Cephalo-pelvic disproportion)
- Forceps
- ICH, depressed fracture

#### B) Neonatal Hypoxia

##### a. CHD

##### b. Respiratory: (RDS...)

##### c. Severe anemia

##### d. Shock

##### e. CNS depression (anomalies, injury, anesthesia)

### Causes of Placental Insufficiency

- ☒ Acute: Placental separation  
(Placenta previa & accidental Hge)
- ☒ Chronic:
  - PIH (Pre-eclampsia)
  - Chronic HTN
  - Advanced DM
  - Placental infarction
  - Placental aging (Post-term)
  - Sickle cell anemia
  - Smoking
  - Drugs: cocaine
  - Idiopathic

### Pathophysiology

1. Hypoxia → anaerobic metabolism → Lactic acidosis
2. Lactic acidosis → ↓↓ glycolysis, ↓↓ cerebral autoregulation & ↓↓ cardiac function →
3. Local ischemia → Energy failure → ↓ Na-K ATPase activity →
4. ↑↑ Intracellular Na, Cl, H<sub>2</sub>O, Ca
5. ↑↑ Extracellular K, excitatory aminoacid neurotransmitters (glutamate & aspartate)
6. Excitatory aminoacids → ↑↑ Intracellular Na, Cl, H<sub>2</sub>O, Ca (↑↑ entry)
7. Immediate neuronal death → Leakage of osmotic materials into the interstitial tissue
8. Vasogenic brain edema → ↑↑ Intracranial pressure → ↑↑ Ischemia (vicious circle)
9. Reperfusion injury

**Pathology (= Topography of brain injury)**

1. Cortical necrosis or infarcts
2. Selective neuronal necrosis
3. Periventricular leukomalacia
4. Subependymal germinal matrix hemorrhage/IVH

Full term

Preterm

**Clinical Picture**

- History suggestive of perinatal asphyxia (obstructed labor, FHR abnormalities, low Apgar...)
- Seizures, apnea, pallor, unresponsiveness...
- Staging of HIE (Sarnat is used in > 36 wk)
- Effects of perinatal asphyxia

**Sarnat staging of HIE**

	Grade 1	Grade 2	Grade 3
Conscious level	Hyperalert	Lethargy	Coma
Pupils	Mydriasis (reactive)	Miosis (reactive)	Unequal or fixed
Posture	Normal	Flexion	Decerebrate
Muscle tone	Normal	Hypotonia	Flaccid
Reflexes/Clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Seizures	No	Common	Decerebrate
EEG	Normal	Low-voltage	Isoelectric
Duration	< 24 hr	1-14 days	Days to weeks
Prognosis	Good	Variable	Death, severe deficits

**Effects of perinatal asphyxia**

System	Effects	Investigations
CNS	HIE ICH Infarction Seizures Brain edema Hypertonia/hypotonia	<ul style="list-style-type: none"> <li>▪ EEG &amp; Amplitude EEG (aEEG)</li> <li>▪ Cranial US</li> <li>▪ MRI, MRS, CT (may be normal on D<sub>1-2</sub>)</li> <li>▪ Visual evoked potentials (VEP)</li> <li>▪ Auditory brain stem response</li> <li>▪ ↑↑ Creatine kinase (brain fraction; CK-BB)</li> </ul>
CVS	Myocardial dysfunction Hypotension Arrhythmias Acidosis	<ul style="list-style-type: none"> <li>▪ ECG (<i>raised ST segment</i>)</li> <li>▪ Echocardiography</li> <li>▪ Myocardial enzymes</li> <li>▪ Blood gases</li> </ul>
Respiratory	PPHN, RDS, MAS Hypoxemia & Acidosis	<ul style="list-style-type: none"> <li>▪ Blood gases</li> <li>▪ CXR</li> </ul>
Renal	ATN & Cortical necrosis Oliguria / Polyuria	<ul style="list-style-type: none"> <li>▪ KFT (BUN &amp; creatinine)</li> <li>▪ Urine osmolality, Fractional excretion of Na</li> </ul>
GIT	Feeding intolerance & NEC Liver damage	<ul style="list-style-type: none"> <li>▪ Occult blood in stools</li> <li>▪ Liver enzymes &amp; LFTs</li> </ul>
Blood	DIC	<ul style="list-style-type: none"> <li>▪ CBC</li> <li>▪ Coagulation profile</li> </ul>
Adrenal	Adrenal hemorrhage	Abdominal US, CT & MRI
Metabolic	↓↓ Glucose, ↓↓ Ca, ↓↓ Na Acidosis, SIADH	Glucose, electrolytes, lactate, blood gases
Skin	SC fat necrosis	

## Management

- A) Antepartum Management (as before) Antepartum assessment of fetal well being
- B) Intrapartum Management (as before) Intrapartum assessment of fetal well being
- C) Postpartum Management

1. Correction of hypoxia (O<sub>2</sub> therapy, ventilation)
2. Moderation of CO<sub>2</sub>
  - a. Hypercapnia → Cerebral VD (Hge)
  - b. Hypocapnia → Cerebral VC (Ischemia)
3. Moderation of BP (loss of cerebral autoregulation) "mean BP = 45-50 mmHg"
  - a. ↓↓ BP → ↓↓ perfusion (Ischemia). Use inotropes to ↑↑ perfusion
  - b. ↑↑ BP → Cerebral Hge
4. Correction of metabolic disturbances (↓↓ Glucose, ↓↓ Ca, ↓↓ Na)
5. Control of seizures: phenobarbitone, phenytoin...
6. Rx of brain edema: fluid restriction, dexamethasone, hyperventilation
7. Cooling: whole body or head cooling (↓↓ energy loss, ↓↓ glutamate release, ↓↓ apoptosis)
8. Cerebroprotective drugs (intervention)
  - a. Selective head hypothermia
  - b. Ca channel blockers
  - c. Antagonists of excitatory aminoacid neurotransmitters receptors
  - d. Free-radical scavengers: Allopurinol & Vitamin E
  - e. VD: Prostacyclin
  - f. Dexamethasone (↑↑ protein synthesis)
  - g. Cyclooxygenase inhibitors (Indomethacin)
  - h. Benzodiazepine receptor stimulation (Midazolam)
9. Management of cardiac effects of asphyxia
  - a. Correction of hypocalcemia & hypoglycemia
  - b. Avoid volume overload
  - c. Inotropes: Dobutamine & Dopamine
10. Management of renal effects of asphyxia
  - a. Monitor urine output
  - b. Avoid nephrotoxic drugs
  - c. Dopamine (renal dose)
11. Management of GIT effects of asphyxia
  - a. Exclude NEC (Occult blood in stools)
  - b. Avoid early feeding
12. Management of Hematologic effects of asphyxia (DIC)
  - a. Transfusion: blood, plasma & platelets
13. Management of pulmonary effects of asphyxia
  - a. Oxygenation & ventilation (M. ventilation, ECMO...)
  - b. Management of PPHN



### Seizures in the 1<sup>st</sup> 24 hr

- ☒ HIE
- ☒ IVH
- ☒ Pyridoxine deficiency
- ☒ Maternal LA
- ☒ Maternal hypotonic IVF
- ☒ Birth injury
- ☒ Neonatal sepsis

### Causes of neonatal coma/dep.:

1. Causes of low Apgar
2. Metabolic (↓↓ G, ↓↓ Ca, ↑↑ Na, ↓↓ Mg, ↑↑ Mg)
3. Infection

## Prognosis

- ☒ Death: 20%
- ☒ Neurological abnormalities (CP, MR...): 30%

## Markers of Poor Prognosis

- Low Apgar at 20 min
- No spontaneous respiration at 20 min
- Sarnat 3
- Early-onset seizures
- Difficult seizure control
- Persistent oliguria (1<sup>st</sup> 36 hr)
- Persistent neurologic signs at 2 weeks
- ↑↑ Intracranial pressure > 10 mmHg
- ↑↑ Creatine kinase (CK-BB)
- aBEG & MRI picture

# Respiratory System

## Transition to Pulmonary Respiration

### Requirements:

- a. Patent airways
- b. Mature RC
- c. Removal of fetal lung fluid
  - ☑ Before birth: Catecholamines, steroids
  - ☑ Vaginal delivery: Intermittent chest compression
  - ☑ After birth: Pulmonary-veins & lymphatics
- d. Creation of functional residual capacity (FRC): "surfactant"

### Causes of First breath

- $\downarrow\downarrow$   $\text{PaO}_2$
- $\uparrow\uparrow$   $\text{PaCO}_2$
- $\downarrow\downarrow$  Body temperature
- Redistribution of CO

## Breathing Patterns

- Regular rhythmic respiration: in full-term neonates
- Periodic breathing: in full-term (during sleep) & Preterm neonates
  - Periodic breathing returns to regular breathing by physical stimulation & Oxygenation
  - Periodic breathing returns to regular breathing by 36 wk post-conceptual age
  - Excellent prognosis

### Periodic breathing:

- Breathing for 10-15 sec at a rate of 50-60/min followed by:
- Apneic pause (5-10 sec)

# Apnea

## Definition

Apnea is cessation of breathing for  $\geq 20$  seconds or any duration if associated with bradycardia & cyanosis

## Incidence (of idiopathic apnea of prematurity)

25% of preterm neonates < 34 wk (1.800 gm)

The majority of preterm neonates < 30 wk

Apnea + Tachycardia = Seizure

## Etiology

### A) idiopathic apnea of prematurity (D<sub>2</sub>-D<sub>7</sub>)

1. Central
  - Developmental immaturity of the respiratory center  $\rightarrow$  Poor function
  - No chest wall movement + No airflow  $\rightarrow$  Paradoxical response to hypoxia
2. Obstructive
  - Upper airway obstruction due to  $\rightarrow$  Passive neck flexion
  - Chest wall movement + No airflow  $\rightarrow$  Pharyngeal instability
3. Mixed (50%)

### B) Symptomatic apnea (See table)

## Monitoring

### Indications:

- a. Preterm neonates < 34 wk (1.800 gm) for at least 1 wk
- b. All neonates with serious diseases (symptomatic apnea)

Method: Monitors with apnea alarm

## Symptomatic Apnea

System	Disease	Clinical Picture	Investigation
CNS	HIE ICH Seizures N/M disorders Anesthesia & sedation	DCL Bulging anterior fontanel Hypertonia/hypotonia Drug history	<ul style="list-style-type: none"> <li>▪ Cranial US</li> <li>▪ CT, MRI, MRS</li> <li>▪ EEG &amp; Amplitude EEG (aEEG)</li> <li>▪ Toxicology screen</li> </ul>
Respiratory	RDS Pneumonia Pneumothorax Obstructive airways	RD (4 grades)	<ul style="list-style-type: none"> <li>▪ CXR</li> <li>▪ Blood gases</li> </ul>
CVS	Heart failure PDA Anemia BP	Tachycardia Murmur	<ul style="list-style-type: none"> <li>▪ CXR</li> <li>▪ ECG</li> <li>▪ Echocardiography</li> </ul>
GIT	Oral feeding GERD NEC Perforation	Feeding difficulties Abdominal distension Signs of feeding intolerance	<ul style="list-style-type: none"> <li>▪ Occult blood in stools</li> <li>▪ Erect abdomen X-ray</li> <li>▪ Barium studies</li> <li>▪ Continuous esophageal pH monitoring</li> </ul>
Metabolic	Hypoglycemia Hypocalcemia ↓ Na & ↑↑ Na Hypothermia & hyperthermia Hyperammonemia Inborn errors of metabolism	Jitteriness Irritability Seizures Acidosis HSM	<ul style="list-style-type: none"> <li>▪ Glucose</li> <li>▪ Electrolytes (Na, K, Ca, Mg)</li> <li>▪ NH<sub>3</sub></li> <li>▪ Blood gases (metabolic diseases)</li> </ul>
Infection	Sepsis Meningitis	Poor reflexes Poor feeding	<ul style="list-style-type: none"> <li>▪ Sepsis screen (CBC, CRP, Cultures...)</li> <li>▪ CSF</li> </ul>
Idiopathic	Immaturity of the RC	Preterm neonate	<ul style="list-style-type: none"> <li>▪ Exclusion</li> </ul>

## Management

1. Check position (obstructive apnea) & repositioning?
2. Tactile stimulation & gentle pharyngeal suctioning
3. Oxygenation (supplemental O<sub>2</sub> or bag & mask)
4. Rx of the cause (symptomatic apnea)
5. Avoid oral feeding
6. Packed RBC (if Hct < 25%)
7. Drug therapy
8. Assisted mechanical ventilation
  - a. Continuous positive-airway pressure (CPAP): Splinting of the airways
  - b. Intermittent mandatory ventilation
  - c. Controlled mechanical ventilation                      prolonged apnea

Drug	Dose	Action	Side Effects	Duration
Theophylline	Loading: 6 mg/Kg/dose Maintenance: 2-4 mg/Kg/dose Route: IV or oral every 6-12 hr	• ↑↑ RC • ↑↑ Diaphragmatic Contractility	• Tachycardia • Irritability • Convulsions	• 36 wk PCA • Control of apnea for 1 wk
Caffeine citrate	Loading: 20 mg/Kg/dose Maintenance: 5 mg/Kg/dose Route: IV or oral every 24 hr	↑↑ RC	• Less toxic	

## Prognosis

- A) idiopathic apnea of prematurity: Usually resolves by 36 wk post-conceptual age  
 B) Symptomatic apnea: Depends on the etiology

# Transient Tachypnea of the Newborn

## Definition

TTN is the most common cause of RD in term neonates

## Etiology

Delayed absorption of fetal lung fluid

TTN is the most common cause of RD in term NB

## Clinical Picture

- Early onset of respiratory distress (4 grades?)
- Chest examination is usually normal

## Investigations

- CXR: Prominent vascular markings  
Inter-lobar fissure edema
- Arterial blood gases

## Course

Rapid recovery within 3 days

## DD

Other causes of RD (RDS, MAS, pneumonia...)

## Treatment

1. Supplemental O<sub>2</sub> (Nasal prongs, head box or incubator O<sub>2</sub>)
2. CPAP may be needed
3. Parenteral or gavage feeding (to avoid aspiration)
4. Antibiotics (*It is not easy to exclude pneumonia*)

No role of diuretic therapy!!



# Respiratory Distress Syndrome

## Incidence

- 60-80% of preterm neonates < 28 wk
- 20-30% of preterm neonates 32-36 wk
- 5% of term neonates

## Risk Factors

Risks ↑ with	Risks ↓ with
• Prematurity	• PIH
• IDM	• Chronic HTN
• CS	• Prolonged ROM
• Asphyxia	• Heroin
• Male sex & 2 <sup>nd</sup> born twin	• Antenatal steroids

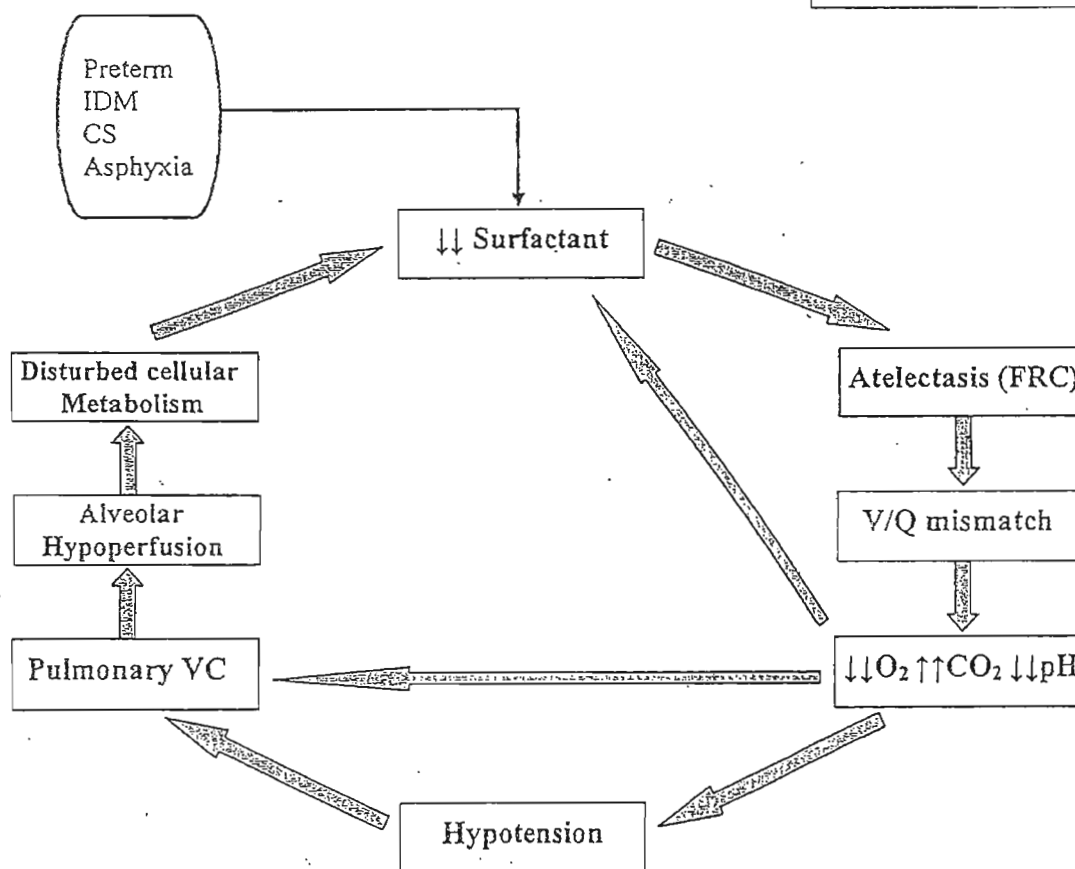
## Pathophysiology (Surfactant Deficiency)

### Surfactant

- **Production:** Alveolar cell type II
- **Maturation:** 35 wks of gestation (L/S ratio??)
- **Function:** ↓↓ Surface tension of the fluid lining the alveoli
- **Constituents:**

### Main Constituents of surfactant:

1. Phosphatidyl choline (lecithin)
2. Phosphatidyl glycerol
3. Surfactant proteins (SP-A, B, C, D)
4. Cholesterol



## Pathology

- a. Gross: Deep purple (liver-like)
- b. Microscopic: alveoli are lined with acidophilic hyaline membrane

### Grades of RD:

1. Tachypnea
2. Retraction & working ala nasi
3. Grunting (forced expiration against closed glottis)
4. Cyanosis

## Clinical Picture

- Onset: minutes\* to hours
- Course: progressive worsening (over 24-72 hr) with gradual improvement in mild cases
- Respiratory distress (4 grades?)
- Chest examination: ↓↓ air entry, bronchial breathing, crepitations & wheezes

## Investigations

- CXR: Reticulo-granular pattern  
Ground-glass appearance  
White lung  
Air bronchogram
- Arterial blood gases: ↓↓ O<sub>2</sub> ↑↑ CO<sub>2</sub> ↓↓ pH
- Blood glucose, electrolytes & CBC
- Antenatal prediction
- Postnatal examination of tracheal aspirate

## DD

Other causes of RD (RDS, MAS, pneumonia...)

## Prevention

### A) Antepartum

- Antenatal care
- Proper assessment of gestational age
- Antepartum assessment of fetal well being
- Assessment of fetal functional maturity (lung maturity, how?)
- Prevention of prematurity??
- Delivery in an equipped hospital
- Antenatal corticosteroids

Steroids: Betamethasone or dexamethasone

Timing: 24-34 wks, 48 hr before delivery

Contraindications: PIH, DM

Advantages: ↓↓ incidence & severity of RDS by ≈40%

**Betamethasone is preferred.**  
Dexamethasone is associated with relative risk of RDS, IVH & Death

### B) Intrapartum Management

- Intrapartum assessment of fetal well being to prevent perinatal asphyxia
- Resuscitation & Stabilization
- Surfactant therapy (Prophylactic or Rescue)

Timing: Immediately after birth or within the 1<sup>st</sup> few hours

Advantages: ↓↓ severity of RDS (But No ↓↓ in the incidence of BPD)

## Monitoring

- a. Clinical: Vital signs, RD, work of breathing, peripheral perfusion, urine output, weight
- b. Laboratory: ABG, electrolytes, blood glucose, Hct

## Management

1. Incubator care of LBW (Temperature control, observation...)

2. Nutrition

a. Parenteral: IVF should be started on D<sub>1</sub>, TPN is used in prolonged cases

b. Enteral: Trophic feeding is started once the neonate is stable

3. Circulation: Vascular access

Volume expanders, +ve inotropes & pressors (dopamine)

4. Antibiotics (*It is not easy to exclude pneumonia*)

5. Correction of acidosis: Metabolic → NaHCO<sub>3</sub> (How?)

Respiratory → Ventilation

6. Respiratory support (Oxygenation & Ventilation)

### Targets:

☒ PaO<sub>2</sub> = 50-70 mmHg

☒ PaCO<sub>2</sub> = 45-55 mmHg

☒ O<sub>2</sub> % = 85-95%

☒ pH = 7.25-7.35

Capillary blood samples are unreliable in assessment of PaO<sub>2</sub> but may be useful in PaCO<sub>2</sub> & pH

Monitoring: Pulse oximetry & ABG →

### Methods:

a. Supplemental oxygen ≥ 60%

b. Nasal CPAP [Pressure = 4-10 cm H<sub>2</sub>O & FiO<sub>2</sub> = 60-100%]

c. Mechanical ventilation: is indicated in

▪ Failure of CPAP

▪ pH < 7.2

▪ PaO<sub>2</sub> < 50 mmHg

▪ PaCO<sub>2</sub> ≥ 60 mmHg

▪ Persistent apnea

▪ ↑↑ Work of breathing

d. High-frequency ventilation

Injury from both hypoxia & hyperoxia should be balanced

Stepwise approach: →

Supplemental oxygen (≥ 60%)

↓  
If still PaO<sub>2</sub> < 50 mmHg

↓  
Nasal CPAP

↓  
If still PaO<sub>2</sub> < 50 mmHg

↓  
Mechanical ventilation

7. Surfactant therapy

☒ Route: Endotracheal (in 4 positions)

☒ Types:

▪ Natural:

Bovine (Survanta)

Porcine (Curosurf)

Calf (Infasurf)

▪ Synthetic (Exosurf)

☒ Strategies:

▪ Prophylactic: for prevention of RDS "more effective"

▪ Rescue: for established RDS

☒ Complications:

▪ Transient hypoxia & bradycardia

▪ ETT obstruction

▪ Pulmonary hemorrhage

Initial ventilatory settings in RDS:

1. FiO<sub>2</sub>: Minimum for adequate oxygenation

2. PIP: 20-25 cm H<sub>2</sub>O

3. PEEP: 4-6 cm H<sub>2</sub>O

4. Rate: 20-60/min

5. IT: 0.4-0.6 sec

6. Flow: 2 L/Kg/min

8. Inhaled Nitric Oxide (iNO)

9. ECMO (*See later*)

- Nitric oxide is an endogenous vasodilator
- It is used in infants with respiratory failure with or without PPHN
- Inhaled NO cause selective pulmonary VD
- iNO ↓↓ PVR & ↑↑ oxygenation

## Complications

### 1. Complications of ETT??

### 2. Complications of umbilical artery catheterization

- Thrombosis, embolism
- Hemorrhage
- Infection
- Reflex arterial vasospasm (leg blanching ± gangrene)
  - Rx: Immediate catheter removal
  - Warm the leg
  - Topical nitroglycerin
  - Intra-arterial tolazoline (1 mg)
- Renovascular hypertension

### 3. Complications of umbilical vein catheterization

- As umbilical artery
- Portal hypertension

### 4. Complication of hyperoxia

- Retinopathy
- Bronchopulmonary dysplasia

### 5. Air leak

- Pneumothorax
- Pneumomediastinum
- Pneumoperitonium
- Pneumopericardium
- Pulmonary interstitial emphysema
- SC emphysema
- Air Embolism

### 6. Anemia

- Frequent sampling
- VA related complications

### 7. PDA

#### C/P:

Apnea  
Hyperdynamic circulation (Big pulse volume)  
Murmur  
Heart failure  
Hepatomegaly

#### Investigations:

#### Rx:

- Adequate oxygenation
- Fluid restriction
- Indomethacin (or ibuprofen; 10-5-5)
- Surgical ligation

### 8. BPD

## Prognosis

A) Mortality is ↓↓ by antenatal steroids, postnatal surfactant, NICU care

B) Mortality is ↑↑ with ↓↓ GA

C) Complications

#### Cause of ↑↑ incidence of PDA:

1. Prematurity
2. Pulmonary hypertension
3. Systemic hypotension
4. Hypoxia
5. Acidosis

#### Lt to Rt shunt ↑ after resolution of RDS. Why?

#### Indomethacin in Rx of PDA

Dose: 0.2 mg/Kg every 12-24 hr

Freq.: 3 doses

Mechanism: ↓↓ PGs

CI: Bleeding

Thrombocytopenia < 50,000

NEC

Oliguria

## Neonatal Respiratory Distress & Failure

### A) Respiratory Causes [RD (4 grades)]

#### a. Airways

- Nose: Choanal atresia
- Mouth: Pierre-Robin syndrome
- Tongue: Macroglossia
- Neck: Goiter & cystic hygroma
- Larynx: Web, cord paralysis, subglottic stenosis & laryngomalacia
- Trachea: Stenosis & laryngotracheomalacia

#### b. Lung parenchyma

- RDS, MAS, TTN, BPD, PPHN
- Pneumonia
- Congenital diaphragmatic hernia
- Congenital lobar emphysema
- Air leak (pneumothorax, mediastinum...)
- Lung hypoplasia (1<sup>ry</sup> or 2<sup>ry</sup>)

### B) Neurological Causes [Shallow, Irregular, Gasping, Apnea, cyanosis]

#### a. CNS

- Maternal drugs
- HIE, ICH
- Congenital malformation
- Apnea

#### b. N/M apparatus

- N/M diseases (Congenital myopathy, Myotonic dystrophy, SMA type 1)

### C) Cardiac Causes

- Heart failure
- PPHN

### D) Hematological Causes

- Anemia
- Polycythemia

### E) Metabolic Causes

- Hypoglycemia
- Hypothermia
- Acidosis

## Extrapulmonary Extravasation of Air (Air Leak)

**Definition** It is air extravasation outside the lungs

Type	Site of air leak	Clinical picture	Investigation
Pneumothorax	Pleural space		X-ray
Pulmonary interstitial emphysema	Pulmonary interstitium	RD, gradual deterioration on M. ventilation	
Pneumomediastinum	Mediastinum	Hypotension, Distant heart sounds, Congested neck veins	
Pneumopericardium	Pericardium	Hypotension, Distant heart sounds	
Pneumoperitoneum	Peritoneum	Usually asymptomatic	
SC emphysema	SC tissue	Crepitus	
Air Embolism	Systemic circulation	Fatal if large amount	

# Respiratory Support

## Forms

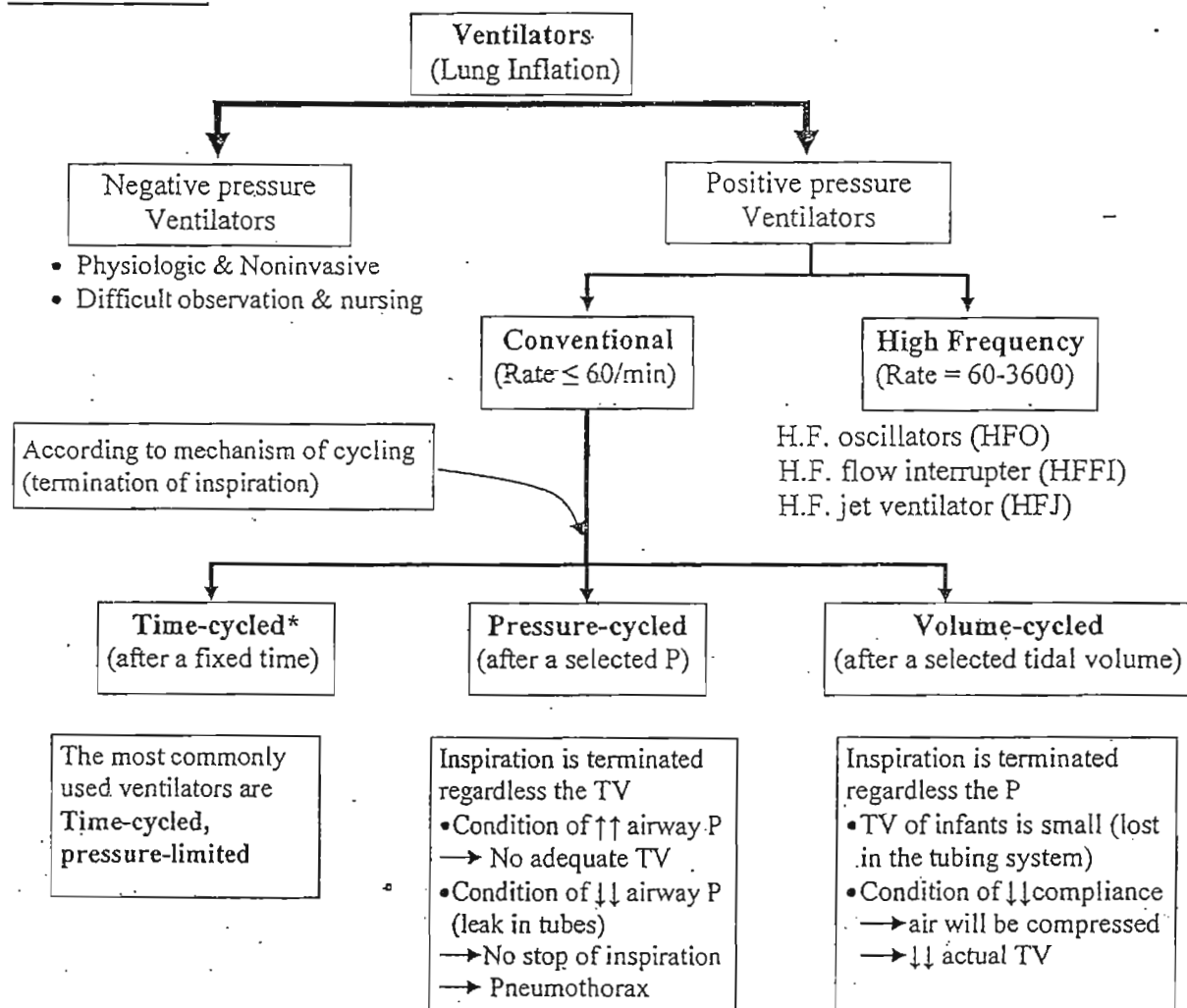
1. Supplemental Oxygen [prongs, box, incubator O<sub>2</sub>]
  2. CPAP (Continuous positive airway pressure)
  3. Positive pressure ventilation
  4. High frequency ventilation
  5. NO (Nitric oxide)
  6. ECMO (Extracorporeal membrane oxygenation)
- } Mechanical Ventilation

## Mechanical Ventilation

### Introduction

Human hand is the best ventilator, but because of human fatigue, mechanical ventilators were invented (*all ventilators are blind*)

### Classification



### Ventilator System

1. Oxygen source
  2. Compressed air source
  3. Mixer → variable O<sub>2</sub> concentration (FiO<sub>2</sub>)
  4. Ventilator → ventilatory support
  5. Humidifier
  6. Patient breathing circuit
- Constant = CPAP  
 → Intermittent = IMV or CMV  
 → Combined = PEEP + IMV or CMV

## Ventilatory Support & Ventilatory Settings

	CPAP (Continuous positive airway pressure)	IMV (Intermittent Mandatory ventilation)	CMV (Controlled Mechanical ventilation)
<b>Function (Action)</b>	<ul style="list-style-type: none"> <li>Keep the airway pressure positive throughout the cycle</li> <li>Splitting of the airways</li> <li>↑↑ FRC</li> <li>Prevention of atelectasis</li> <li>↓↓ work of breathing</li> </ul>	<ul style="list-style-type: none"> <li>Partial intermittent support</li> <li>Only some breaths are given</li> <li>These breaths may be triggered by the patient own inspiration (SIMV)</li> <li>↓↓ work of breathing</li> </ul>	<ul style="list-style-type: none"> <li>Total intermittent support</li> <li>Usually combined with PEEP</li> </ul>
<b>Patient's Breathing</b>	Spontaneous	Spontaneous	Absent or ineffective
<b>Indications</b>	<ul style="list-style-type: none"> <li>↓↓ Oxygenation (in spite of supplemental O<sub>2</sub>)</li> <li>Mild RDS</li> <li>Moderately frequent apnea</li> <li>Wearing from M. Ventilation</li> <li>↑↑ work of breathing</li> </ul>	<ul style="list-style-type: none"> <li>Failure of CPAP to ↑↑ oxygenation &amp; ↓↓ work of breathing (Pa O<sub>2</sub> &lt; 50)</li> <li>PaCO<sub>2</sub> ≥ 60 mmHg (Hypoventilation)</li> <li>pH &lt; 7.2</li> <li>Shock</li> <li>Coma</li> </ul>	<ul style="list-style-type: none"> <li>Persistent apnea</li> <li>Type II respiratory failure</li> <li>Failure of CPAP &amp; IMV</li> <li>pH &lt; 7.2</li> <li>PaO<sub>2</sub> &lt; 50 mmHg</li> <li>PaCO<sub>2</sub> ≥ 60 mmHg</li> </ul>
<b>Methods</b>	Nasal, Nasopharyngeal or ETT	ETT	ETT
<b>Ventilatory settings</b>	<ul style="list-style-type: none"> <li>FiO<sub>2</sub> = 40-100%</li> <li>Pressure = 4-10 cm H<sub>2</sub>O</li> </ul>	FiO <sub>2</sub> , Rate, Inspiratory time (IT), Expiratory time, I/E ratio, Flow, Tidal volume, Peak inspiratory pressure (PIP), Positive end expiratory pressure (PEEP)	
<b>Assessment</b>	Oxygenation & work of breathing	Oxygenation, ventilation & work of breathing	Oxygenation & ventilation
<b>Complications</b>	<ul style="list-style-type: none"> <li>Gastric distension (insert gastric tube)</li> <li>Nasal septal injury</li> <li>Feeding difficulties</li> <li>Air leak (pneumothorax)</li> <li>↑↑ Intrathoracic P → ↓↓ VR, ↓↓ BP, ICH</li> </ul>	Complications of Mechanical Ventilation	

### Settings to improve Oxygenation

- ↑↑ FiO<sub>2</sub>
- ↑↑ PEEP

### Settings to improve Ventilation

- ↑↑ Rate
- ↑↑ PIP
- ↑↑ Tidal volume [TV = Flow x IT]

### Assessment of Oxygenation

- Color: Pink
- PaO<sub>2</sub>
- O<sub>2</sub> Saturation

### Assessment of Ventilation

- Chest expansion
- Air entry
- PaCO<sub>2</sub>

## Complications of Mechanical Ventilation

	Complications	How to avoid
<b>ETT</b>	<ul style="list-style-type: none"> <li>Injury (oral cavity, nose, vocal cord, larynx)</li> <li>Obstruction</li> <li>Malposition</li> <li>Infection</li> </ul>	<ul style="list-style-type: none"> <li>Careful intubation</li> <li>Suction</li> <li>Proper fixation (check position)</li> <li>Aseptic precautions</li> </ul>
<b>Ventilator</b>	<ul style="list-style-type: none"> <li>Power failure</li> <li>Disconnection</li> <li>Kinking</li> <li>Humidifier water loss</li> </ul>	Check
<b>Settings</b>	<ul style="list-style-type: none"> <li>↑↑ Pressure (PIP or PEEP) → air leak</li> <li>↑↑ PEEP → ↓↓ VR → ↓↓ CO + ↑↑ ICP</li> <li>↑↑ Inspiratory time</li> <li>↓↓ Expiratory time</li> </ul>	Avoid high or inappropriate settings
<b>Patient</b>	<ul style="list-style-type: none"> <li>Fighting</li> <li>Self extubation</li> <li>Feeding</li> <li>Underlying pathology</li> </ul>	<ul style="list-style-type: none"> <li>Sedation (Fentanyl, midazolam...)</li> <li>Muscle paralysis (pancuronium)</li> <li>Parenteral nutrition</li> <li>Adjust settings according to pathology</li> </ul>

### Causes of deterioration of blood gases

#### A) Sudden

1. ETT: displacement or obstruction
2. Ventilator: power failure
3. Low pressure
4. Circuit: Disconnection or leak
5. Air leak (pneumothorax...)
6. Massive lung collapse
7. Cardiac compromise (↓↓ VR)
8. CNS: ICH

#### B) Gradual

1. ETT: partial obstruction
2. Partial lung collapse (more on the Rt side)
3. Lack of physiotherapy
4. Infection
5. Anemia
6. PDA
7. BPD
8. Fighting

### Mechanical ventilation in specific diseases

#### A) ↓↓ Compliance (RDS & pneumonia)

- ↑↑ Inspiratory time (I/E = 1:2 or even 1:1)
- ↑↑ PEEP

#### B) ↑↑ Airway pressure (MAS & asthma)

- ↑↑ Expiratory time (I/E = 1:3 or even 1:4)
- ↓↓ PEEP ≤ 4 cm H<sub>2</sub>O

#### C) Air leak (pneumothorax)

- ↑↑ FiO<sub>2</sub> & ↓↓ PIP, PEEP
- HFV

### Causes of Air leak (pneumothorax)

1. ↑↑ Pressure (PIP or PEEP)
2. ↑↑ IT
3. ↓↓ Expiratory time
4. ETT malposition (usually into Rt lung)
5. Improved lung pathology without ↓↓ settings
6. Unilateral lung pathology
7. Inadequate humidification
8. Aggressive physiotherapy



## High Frequency Ventilators

### Description

Extremely rapid rates with small tidal volumes (< dead space)

### Types

HFO, HFJ, HFEI

### Advantages

- ↓↓ Barotrauma (lung injury)
- Recruitment of collapsed alveoli
- Useful in air leak (pneumothorax...)

### Disadvantages

- Complex & expensive
- No statistically significant difference in outcome

## Extracorporeal membrane oxygenation ECMO

### Definition

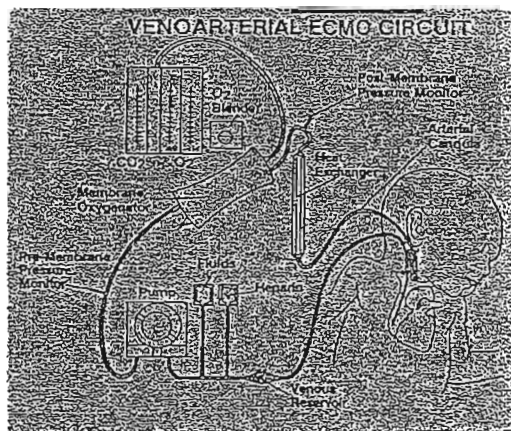
It is a form of cardiopulmonary bypass that augments systemic perfusion & provides gas exchange; so allows lung to recover "lung rest"

### Indications (Severe cardiorespiratory failure)

- PPHN
- MAS
- RDS
- Congenital diaphragmatic hernia
- Heart disease
- Sepsis

### Technique

- Two VA (IJV & Carotid artery)
- Venous blood is drained from the IJV, pumped through a membrane oxygenator "artificial lung" which extracts CO<sub>2</sub> & adds O<sub>2</sub>
- The blood is then returned to the baby through an artery
- The lungs are still mechanically ventilated but at low settings



### Complications

- Bleeding (heparin): IVH...
- Thrombosis & embolism
- Thrombocytopenia
- Infection
- Ischemic brain injury (due ligation of carotid artery)

## Inhaled Nitric Oxide

- ☑ Nitric oxide is an endogenous vasodilator
- ☑ Used in infants with respiratory failure with or without PPHN
- ☑ Inhaled NO cause selective pulmonary VD
- ☑ NO lowers pulmonary vascular resistance & ↑↑ oxygenation

# Bronchopulmonary Dysplasia

## Definition

BPD is lung injury in neonates requiring mechanical ventilation & supplemental O<sub>2</sub> for Rx of respiratory failure (RDS\*)

## Incidence (Variable according to definition used)

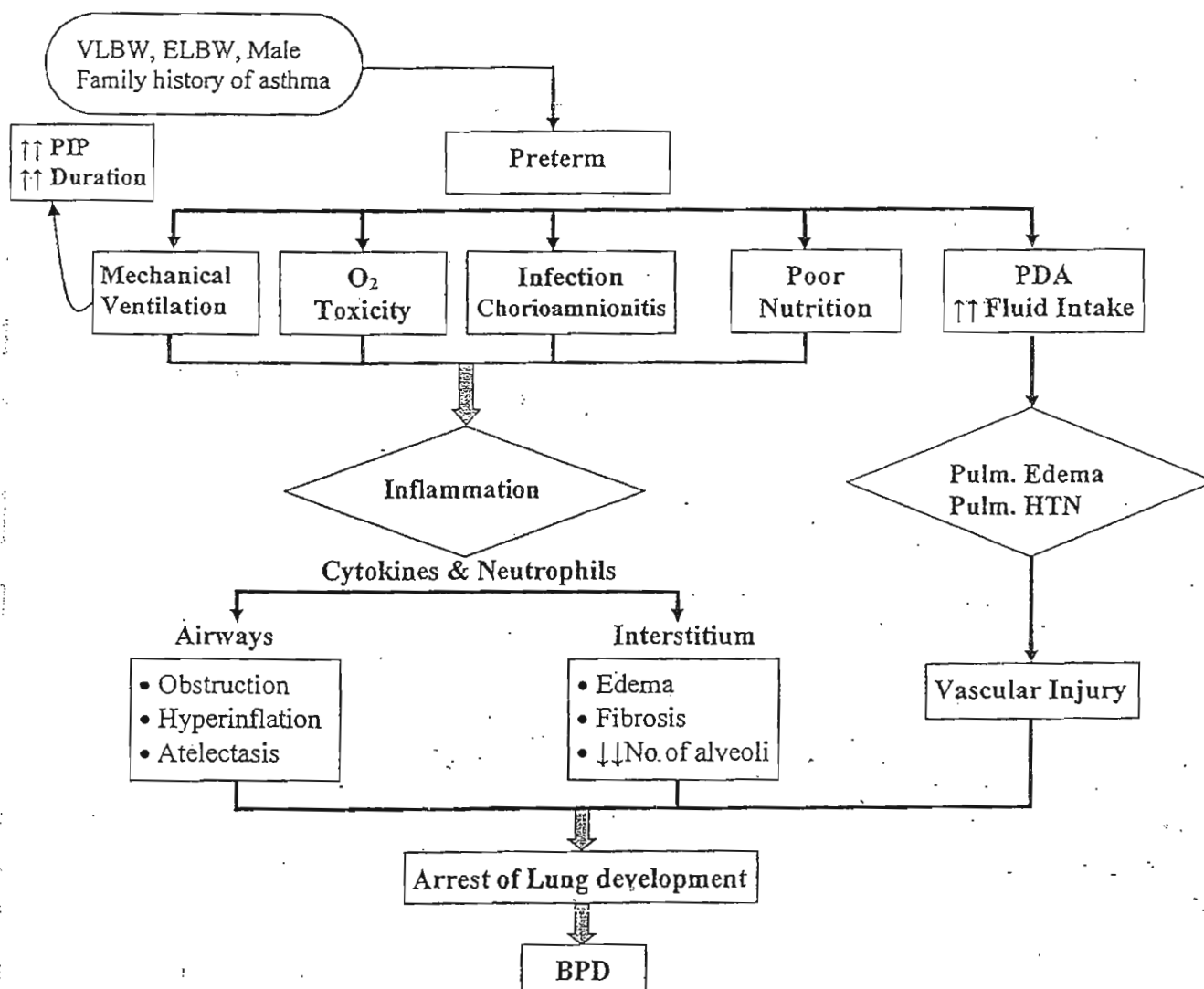
The most susceptible group is neonates < 1.250 gm  
It is relatively uncommon in neonates > 32wk

The term BPD should be used rather than chronic lung disease (CLD)

## Diagnostic Criteria

		≤ 32 wk	> 32 wk
Time of assessment		<ul style="list-style-type: none"> <li>• 36 wk PMA</li> <li>• Discharge</li> </ul>	<ul style="list-style-type: none"> <li>• 56 days</li> <li>• Discharge</li> </ul>
Essential criterion		Rx with > 21% O <sub>2</sub> for ≥ 28 days PLUS	
At Time of assessment	Mild BPD	Breathing room air	
	Moderate BPD	Needs < 30% O <sub>2</sub>	
	Severe BPD	Needs ≥ 30% O <sub>2</sub> or PPV	

## Pathophysiology (= risk-factors + pathogenesis)



## Pathology

- a. Acute phase: edema, cellular infiltration & release of cytokines
- b. Chronic phase: fibrosis & obliterative bronchiolitis

## Clinical Picture

- Respiratory distress (4 grades?)
- Prolonged mechanical ventilation & O<sub>2</sub> therapy "O<sub>2</sub> dependence"
- Heart failure
- Chest examination: wheezes & crepitations

## Investigations

- Arterial blood gases: hypoxia, hypercapnia & acidosis
- CXR: Early → RDS  
Then → areas of atelectasis, hyperinflation & cyst formation
- Echocardiography: PDA, pulmonary HTN & Rt ventricular hypertrophy

## Prevention

1. Antenatal steroid therapy (Betamethasone)
2. Postnatal surfactant therapy (prophylactic therapy is more effective)
3. Vitamin A "↑↑ epithelial repair" (5.000 IU, IM, 3 times/week)
4. Rx of PDA
5. Avoid excess IVF
6. Ventilatory settings (avoid high PIP)
7. High-frequency ventilation

## Monitoring

- a. Clinical: vital signs, RD, work of breathing, peripheral perfusion, urine output, weight
- b. Laboratory: ABG, electrolytes, blood glucose, Hct

## Treatment

1. Nutrition
  - ↑↑ Caloric intake
  - Supplementation with Vitamin A & vitamin E "anti-oxidant"
  - Trace elements (Se, Zn, Cu)
2. Fluid restriction
3. Diuretic therapy
  - Furosemide or hydrochlorothiazide ± spironolactone
4. Dexamethasone "Anti-inflammatory"
  - Short course of low dose (0.25 mg/Kg/day for 5-7 days)
  - ↓↓ O<sub>2</sub> requirements, ↓↓ ventilatory settings, facilitates extubation & ↓↓ post-extubation laryngeal edema
  - Side effects: HTN, hyperglycemia, GIT bleeding & perforation, sepsis & ↑↑ risk of CP
5. Bronchodilators: Inhaled β<sub>2</sub> agonists
6. Respiratory support
  - Chest physiotherapy & suctioning
  - O<sub>2</sub> & mechanical ventilation to maintain satisfactory oxygenation
7. Inhaled Nitric Oxide (iNO)
8. Blood transfusion
9. Rx of infection
10. Rx of PDA

The routine use of dexamethasone is Not recommended

PaO<sub>2</sub> = 50-70 mmHg  
PaCO<sub>2</sub> = 50-70 mmHg  
pH > 7.3

## Home Treatment

1. Nutrition (↑↑ Caloric intake)
2. Diuretic therapy
3. Bronchodilators
4. Immunization
  - Routine immunization
  - Pneumococcal vaccine
  - Influenza vaccine
  - Monoclonal Ab against RSV (Palivizumab)
5. Avoid passive smoking

## Complications

1. Growth failure
2. Systemic HTN, pulmonary HTN, LV hypertrophy, RV hypertrophy
3. Airway hyperreactivity
4. Complications of medications:
  - ☒ Furosemide (Hypokalemia & nephrocalcinosis)
  - ☒ Dexamethasone?
  - ☒ Antibiotics
  - ☒ O<sub>2</sub>: ROP

## Prognosis

- Recovery within 6-12 months (in surviving neonates)
- Mortality 20% (respiratory failure, infection , cardiac complications)
- Complications

# Aspiration of Foreign Material Syndrome

## Etiology

1. MAS
2. Aspiration of milk or medications
  - Immaturity (uncoordinated reflexes)
  - Improper feeding
  - RD, TOF, GERD, CP

## Clinical Picture

Choking & aspiration pneumonia

## Investigations

- CXR
- Bronchoscopy

## Treatment

- Respiratory support
- Rx of pneumonia
- Bronchoscopy

# Meconium Aspiration Syndrome

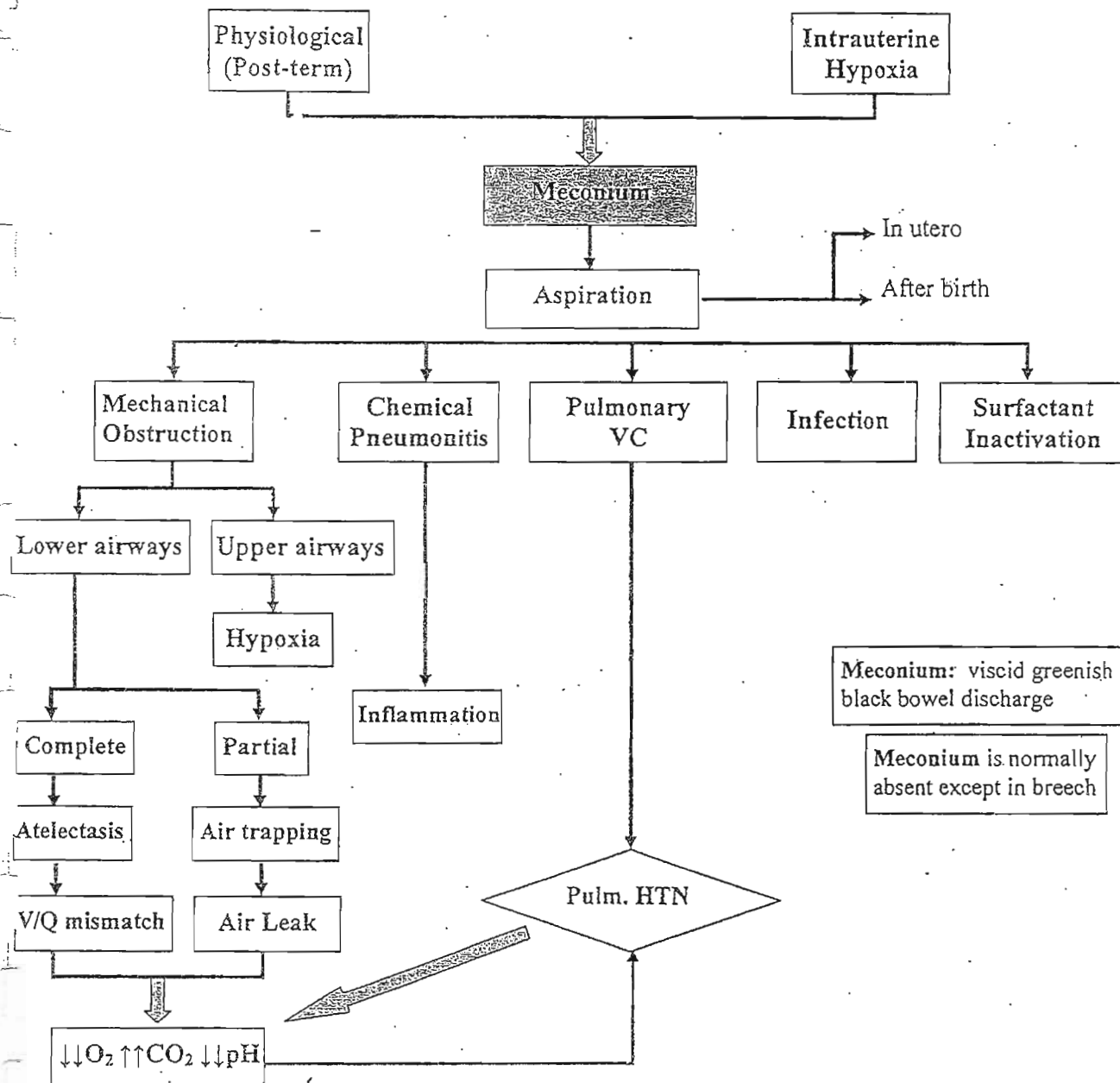
## Definition

MAS is RD in a neonate borne through meconium-stained amniotic fluid (MSAF) whose symptoms can not be otherwise explained

## Incidence

- MSAF occurs in 13% of all deliveries
- MAS occurs in 5% of MSAF

## Pathophysiology



## Clinical Picture

- Onset: within few hours
- MSAF
- Respiratory distress (4 grades?)
- Chest examination: ↓↓ air entry, bronchial breathing, crepitations & wheezes

## Investigations

- CXR: Patchy infiltrates  
Hyperinflation ( $\uparrow\uparrow$  AP diameter + Flat diaphragm)  
Air leak (pneumothorax)
- Arterial blood gases:  $\downarrow\downarrow$   $O_2$   $\uparrow\uparrow$   $CO_2$   $\downarrow\downarrow$  pH

**DD** Other causes of RD (RDS, pneumonia...)

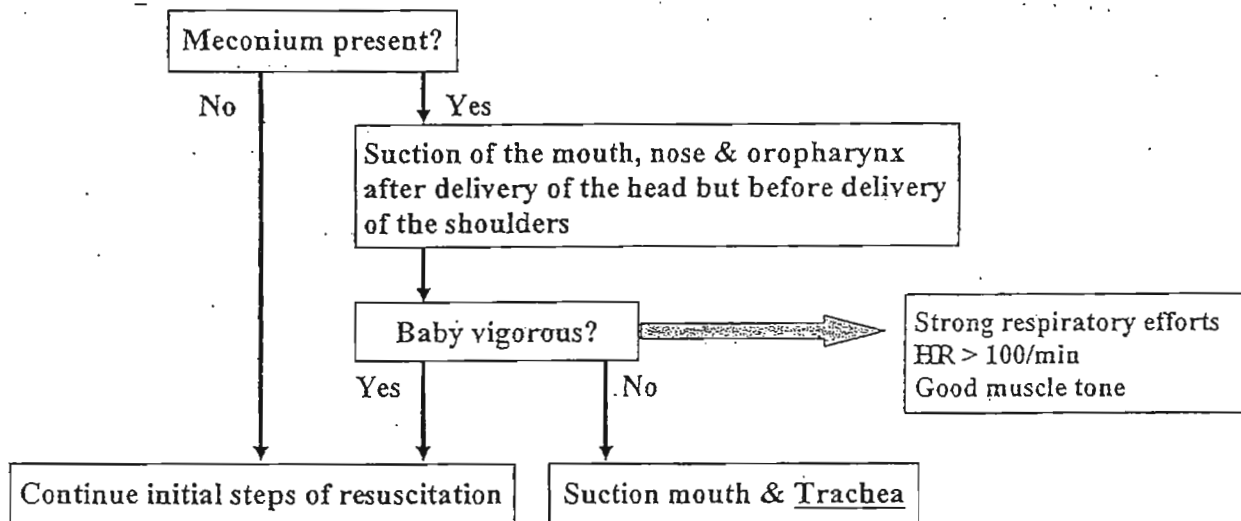
## Prevention

### A) Antepartum

- Antenatal care
- Proper assessment of gestational age
- Antepartum assessment of fetal well being (placental insufficiency)
- Delivery in an equipped hospital

### B) Intrapartum Management

- Intrapartum assessment of fetal well being
- Management of MSAF



## Monitoring

- Clinical:** vital signs, RD, work of breathing, peripheral perfusion...
- Laboratory:** ABG, electrolytes, blood glucose, Hct

## Treatment

1. Incubator care (Temperature control, observation...)
2. Respiratory support
  - Frequent chest physiotherapy & suctioning
  - Supplemental oxygen
  - Nasal CPAP
  - Mechanical ventilation
3. Antibiotic
4. Rx of pulmonary hypertension
5. Rx of air leak
6. Surfactant therapy
7. Inhaled Nitric oxide
8. ECMO

Mechanical ventilation is risky, but often required!

## Persistent Pulmonary Hypertension of the NB (Persistent Fetal Circulation - PPHN)

### Definition

It is persistent elevation of the pulmonary vascular resistance after birth with Rt to Lt shunt across:

- a. Patent foramen ovale
- b. PDA

### Incidence

- PPHN occurs in 1:1000 (more in term & post-term)
- Mortality = 50%

### Etiology

#### A) Pulmonary VC

1. Perinatal asphyxia
2. Pulmonary parenchymal diseases: RDS, MAS, diaphragmatic hernia
3. CNS causes (Hypoventilation)
4. Sepsis
5.  $\downarrow\downarrow$  Ca,  $\downarrow\downarrow$  Glucose & acidosis

#### B) Pulmonary vascular smooth muscle hypertrophy: Chronic IU hypoxia

#### C) Myocardial depression

1. HIE
2. Myocarditis
3. Sepsis
4. Polycythemia
5.  $\downarrow\downarrow$  Ca,  $\downarrow\downarrow$  Glucose & acidosis

#### D) Sepsis (Why?)

#### E) $\downarrow\downarrow$ Cross sectional area of pulmonary vascular bed

1. 1<sup>st</sup> pulmonary hypoplasia
2. 2<sup>nd</sup> pulmonary hypoplasia (Potter's syndrome)
3. Congenital diaphragmatic hernia
4. Alveolar capillary dysplasia (Fatal)

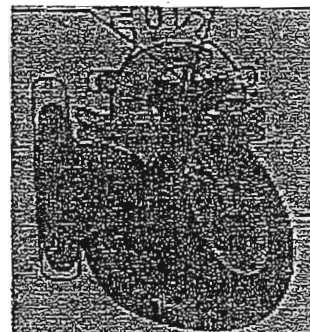
#### F) Idiopathic

### Pathology

- Pulmonary vasospasm
- Pulmonary hypoplasia
- Pulmonary vascular remodeling ( $\uparrow\uparrow$  Medial thickness)

### Clinical Picture

- Onset: within few hours
- Respiratory distress (4 grades?)
- Cyanosis
- Single accentuated S<sub>2</sub>
- Pulse oximeter readings in the UL & LL??
- Hyperoxia test



PPHN should be suspected in the presence of any risk factor

#### Hyperoxia test

- 100% O<sub>2</sub> for 10 min (Head box)
- ABG (PaO<sub>2</sub>) before & after O<sub>2</sub>
- If PaO<sub>2</sub> > 110 mmHg  
CHD is unlikely  
Lung disease or PPHN
- If PaO<sub>2</sub> < 110 mmHg  
CHD is likely  
Severe lung disease or PPHN

### DD Other causes of RD & cyanosis (RDS, pneumonia...) & CHD

[CHD: Cardiomegaly, murmur (grade 3), weak pulse, hyperoxia test...]

## Investigations

- CXR: Minimal findings (normal lung fields + normal cardiac shadow)
- Arterial blood gases:  $\downarrow\downarrow$   $O_2$   $\uparrow\uparrow$   $CO_2$   $\downarrow\downarrow$  pH
- Echocardiography:
  - CHD, cardiac contractility, PDA
  - Direction of flow across PFO & PDA
  - Estimation of pulmonary pressure

## Treatment

1. Incubator care (Temperature control, observation...)
2. Respiratory support
  - Supplemental oxygen (100%  $O_2$ )
  - Mechanical ventilation (if failure of 100%  $O_2$ )
  - HFV (if failure of conventional mechanical ventilation)
3. Positive inotropic agents
  - Dopamine
  - Dobutamine
4. Correction of  $\downarrow\downarrow$  Ca,  $\downarrow\downarrow$  Glucose, acidosis & polycythemia
5. Tolazoline ( $\alpha$  receptor antagonist): pulmonary VD [Side effect = systemic hypotension]
6. Sildenafil (*Viagra*)
7. Prostacyclin
8. Surfactant therapy
9. Inhaled Nitric oxide
10. ECMO

$PaO_2 = 80-100$ mmHg $PaCO_2 = 35-45$ mmHg <ph 7.35-7.45="" <="" =="" td=""> </ph>
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## Prognosis

- Mortality  $\approx$  50%
- Related to the etiology (pulmonary hypoplasia, diaphragmatic hernia...)



# Pneumothorax

## Definition

It is the presence of air within the pleural space

## Incidence

- Asymptomatic\*: 1-2% of all newborn infants
- Symptomatic

## Etiology

### A) Spontaneous

### B) Secondary

#### ☒ Lung diseases

- RDS, MAS, BPD
- Lung cysts (congenital or acquired)
- Lung hypoplasia (1<sup>ry</sup> or 2<sup>ry</sup>)
- Congenital diaphragmatic hernia
- Congenital lobar emphysema
- Pneumatocele

#### ☒ Traumatic

- Barotrauma (ambu-bag or mechanical ventilation). Risk factors
- Vigorous resuscitation or physiotherapy
- Vascular access insertion "pleural injury"
- Chest surgery
- Accidental trauma (penetration wounds)

### Causes of Air-leak (pneumothorax)

1. ↑ P Pressure (PIP or PEEP)
2. ↑ P<sub>pl</sub>
3. ↑ Expiratory time
4. ETT malposition (usually into Rt lung)
5. Improved lung pathology without E settings
6. Unilateral lung pathology
7. Inadequate humidification
8. Aggressive physiotherapy

### Lung Cysts

- ☒ Congenital
- ☒ Acquired\*

#### C/P:

- Asymptomatic
- Rupture → Pneumothorax

#### Rx:

- Conservative
- Surgical removal

## Clinical Picture

- Asymptomatic
- Respiratory distress (4 grades?)
- Chest examination:
  - Unilateral bulge
  - Mediastinal shift
  - Hyper-resonance
  - ↓↓ air entry
- May be bilateral in 10%
- Tension pneumothorax → Collapse of the ipsilateral lung  
Compression of the opposite lung  
↓↓ VR, ↓↓ BP, Obstructive shock

## Investigations

- CXR: Jet-black translucency + Mediastinal shift
- Needle aspiration (2<sup>nd</sup> intercostals space MCL): "Diagnostic Therapeutic test"

## Treatment

- Conservative management (if asymptomatic): Observation + 100 % O<sub>2</sub>
- Needle aspiration
- Chest tube with underwater-seal drainage
- HFV is the ventilatory treatment of choice

## Complications

- Respiratory failure
- Obstructive shock
- ICH (↑↑ Intra-thoracic pressure)
- SIADH

# Surgical Emergencies in the NB

## I. Fetal manifestation

1. Polyhydramnios: TOF, Intestinal obstruction, hydrocephalus
2. Oligohydramnios: Obstructive uropathy (PUV)...
3. Dytocia: Hydrops
4. Fetal ascites: Obstructive uropathy, hydrops, thoracic duct obstruction, CHD

## II. Neonatal manifestation

### 1. Respiratory distress

- ☒ Choanal atresia
- ☒ TOF
- ☒ Congenital lobar emphysema
- ☒ Congenital diaphragmatic hernia

Intubate with ETT

### 2. Scaphoid abdomen: Congenital diaphragmatic hernia

### 3. Abdominal distension

- ☒ Pneumoperitoneum (= perforated viscus; stomach, intestine...)
- ☒ Intestinal obstruction

NGT is mandatory

#### • Congenital IO

- Duodenal atresia, annular pancreas, fibrous band of Ladd
- Jejunal, ileal atresia
- Malrotation, volvulus
- Imperforate anus, Hirschsprung disease

#### • Acquired IO

- Functional "paralytic ileus": RDS, sepsis, NEC
- Organic "mechanical": Intussusception, strangulated inguinal hernia, NEC

### 4. Abdominal wall defects (Omphalocele & gastroschisis)

	Omphalocele	Gastroschisis
Defect	Umbilicus	To the RT of the umbilicus
Relation to the cord	Inside the cord	To the RT of the cord
Coverings	Peritoneal membrane & amnion	No coverings
Diagnosis	Antenatal US screening	
Treatment	NGT + NPO + IVF (TPN may be needed) Wrapping with warm, sterile, saline soaked gauze (↓ heat loss & protection) Surgical repair	

### 5. Excessive salivation: TOF

### 6. Vomiting (see before)

### 7. Hematemesis & bloody stools

- ☒ NEC
- ☒ Gastric stress ulcer
- ☒ Swallowed maternal blood →

### 8. Abdominal mass

### 9. Inguinal hernia

### 10. Birth injury (fractures, ICH, solid organ injury)

### 11. Failure to pass meconium (IO, imperforate anus)

### 12. Failure to pass Urine (Obstructive uropathy e.g., PUV)

<b>Apt test:</b> Test done in GI bleeding to detect maternal RBCs
<b>Kleihauer test:</b> Test on maternal blood to detect fetal RBCs

# Digestive System

## Neonatal Vomiting

### Etiology

#### A) Well-doing baby

1. Amniotic gastritis
2. Swallowed maternal blood
3. Feeding disorders
  - Wrong feeding & overfeeding,
  - Failure of eructation
  - ↑↑ Manipulation
4. GERD: following meals, related to posture
5. CHPS: Usually starts in the 2<sup>nd</sup> or 3<sup>rd</sup> week, projectile; shortly after meals, never bilious  
 Pyloric mass may be palpated, diagnosed by US, barium meal  
 More common in ♂  
 Rx: pyloromyotomy (Ramstedt's operation)
6. Cow's milk protein allergy

#### B) Sick baby

1. Tracheoesophageal fistula (TOF) (1<sup>st</sup> feed)
2. Congenital intestinal obstruction (e.g., atresia...)
3. Acquired intestinal obstruction (e.g., Intussusception...)
4. Ileus (RDS, sepsis, NEC...)
5. ↑↑ Intracranial tension: HIE, ICH, meningitis
6. Inborn errors of metabolism:
  - Urea cycle defects
  - Organic acidemia
  - Galactosemia
  - CAH

**VATER/VACTERL**  
 Vertebral, Anorectal, Cardiac, Trachea,  
 Esophagus, Renal, Limb

## Neonatal Constipation [Failure to pass stool for > 36 hrs]

#### 1. Since birth

- Causes of intestinal obstruction...
- Meconium plug
- Meconium ileus
- Hirschsprung disease

#### 2. Not presenting at birth

- Hirschsprung disease
- Hypothyroidism

#### Meconium plug:

Structure: Low water content  
 Risk factors: IDM, CF, MgSO<sub>4</sub>  
 C/P: IO

#### Rx:

- Glycerin suppositories
- Enema (Saline or gastrographin)
- Surgical removal

## Neonatal Diarrhea (GIT)

### Oral Candidosis

1. Maternal transmission: vaginal, breast
2. Prolonged antibiotics
3. T-cell dysfunction
4. HIV infection

#### Meconium ileus (CF):

C/P: IO, peritonitis

#### Rx:

- Glycerin suppositories
- Enema (Saline or gastrographin)
- Surgical

#### Meconium peritonitis:

Etiology: M. ileus or M. plug  
 C/P: IO, perforation  
 Rx: Surgical drainage

# Necrotizing Enterocolitis (NEC)

## Definition

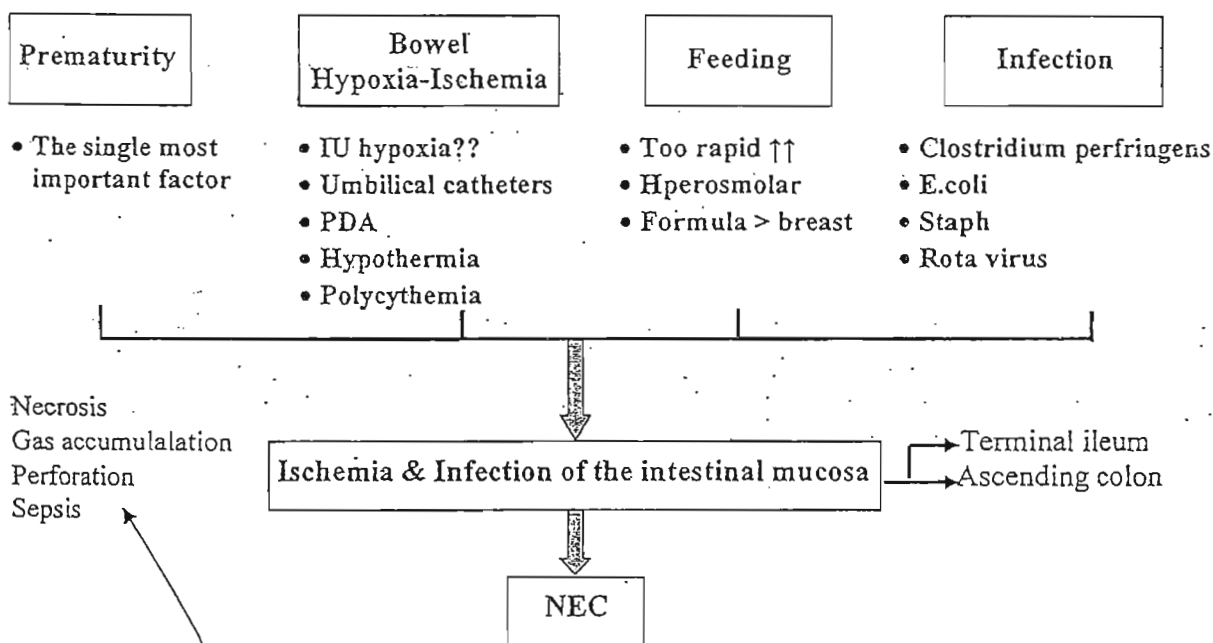
NEC is a syndrome of acute intestinal inflammation & necrosis

## Incidence

The most susceptible group is neonates 30-32 wks

10% are full-term

## Pathophysiology (= risk factors + pathogenesis)



## Pathology

High index of suspicion

## Clinical Picture (Onset = 1-2 wks)

### A) Systemic signs

- RD or apnea
- Temperature instability
- Hypotension, poor perfusion, shock
- Lethargy, poor feeding
- Bleeding tendency
- Acidosis

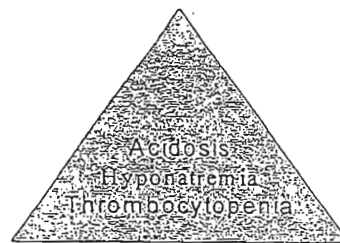
### B) Local (Abdominal) signs

- Feeding intolerance??
- Abdominal distension & tenderness
- Signs of peritonitis/perforation
  - Abdominal distension
  - Abdominal wall edema
  - Abdominal wall discoloration
  - Absent intestinal sounds "ileus"
  - Ascites

1. Bilious or bloody gastric residue
2. ↑↑ Residue (>25% of the previous feed)
3. ↑↑ Abdominal girth
4. Vomiting
5. Bloody stools
6. Watery stools

## Investigations

- CXR:
  - Dilatation of intestinal loops
  - Intestinal wall edema
  - Intramural air (pneumatosis intestinalis)
  - Pneumoperitoneum
  - Portal vein air
- Blood: Triad of metabolic acidosis, hyponatremia & thrombocytopenia
- Stool analysis: Gross or occult blood in stools



## Bell Staging Criteria

Stage I = Clinical symptoms & signs

Stage II = Clinical symptoms & signs + pneumatosis intestinalis

Stage III = Clinical symptoms & signs + pneumatosis intestinalis + critically ill

## Prevention

1. Prevention of prematurity
2. Antenatal steroid therapy (↓↓ incidence of NEC)
3. Use breast milk
4. Avoid hyperosmolar feeds
5. Avoid rapid ↑↑ in feed volume (not > 15-20 cc/Kg/day)
6. Prebiotics & probiotics (trials)

## Monitoring

- a. Clinical: vital signs, abdominal signs, RD, peripheral perfusion, urine output, weight
- b. Laboratory: ABG, electrolytes, blood glucose, Hct, serial X-ray

## Treatment

### I. Medical treatment

#### 1. Nutrition

- ☒ NPO & TPN
- ☒ Initiation of feeding (2-week bowel rest): Trophic feeding with breast milk
- ☒ Monitor signs of feeding intolerance

#### 2. Supportive measures

- ☒ Removal of umbilical catheters
- ☒ Respiratory: Airway, Supplemental O<sub>2</sub> or mechanical ventilation may be needed
- ☒ CVS: Rx of shock, hypotension, Dopamine (2-5 µg/Kg/min): ↑↑ splanchnic blood flow
- ☒ Metabolic: correction of acidosis & electrolyte disturbances
- ☒ Blood: whole blood, platelet transfusion, vitamin K supplementation

#### 3. Antibiotics (*broad-spectrum*): Ampicillin + Gentamicin + Clindamycin

Adjust the antibiotics according to the results of cultures (blood, stool...)

### II. Surgical

#### Indications:

- ☒ Intestinal perforation
- ☒ Failure of medical treatment

#### Options:

- ☒ Peritoneal drainage
- ☒ Resection-anastomosis

## Complications

- Electrolyte disturbances, DIC, sepsis
- TPN
- Stricture & enteric fistula
- Short bowel syndrome (diarrhea & FTT)

# Neonatal Jaundice

## Definition

Neonatal jaundice is yellowish discoloration of the skin & mucous membrane  
Clinical jaundice appears when bilirubin level is  $> 7 \text{ mg \%}$  (In adults if  $> 2 \text{ mg \%}$ )

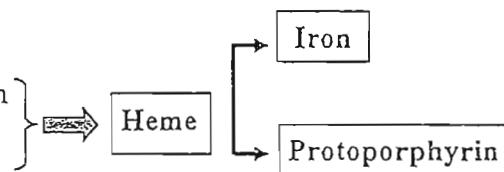
## Incidence

60% of full-term & 80% of preterm neonates develop jaundice in the 1<sup>st</sup> week of life  
It may be caused by very mild or very serious condition that should be identified

## Bile Pigments Metabolism

### 1. Production of bilirubin

- ☑ Old RBCs  $\rightarrow$  Hemoglobin  $\rightarrow$  Heme + Globin
- ☑ Myoglobin
- ☑ Heme-containing enzymes (e.g., CYP<sub>450</sub>)



Protoporphyrin  $\rightarrow$  Bilivirdin  $\rightarrow$  Bilirubin  $\rightarrow$  circulation "UCB or Hembilirubin"

### 2. Transport

- Unconjugated bilirubin (UCB) is bound to albumin (No renal excretion + No CNS)

### 3. Uptake of bilirubin

- Uptake by the liver (by proteins X & Y)

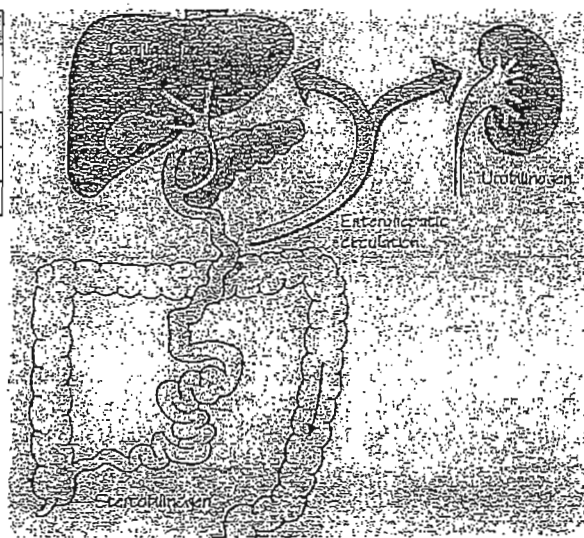
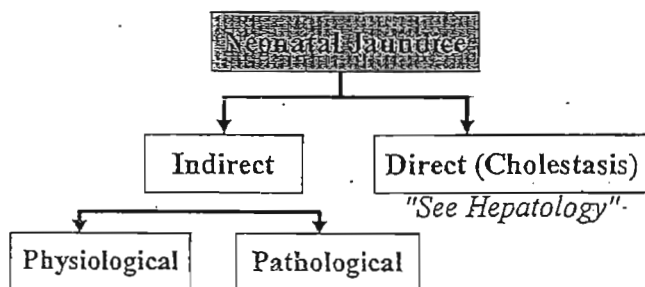
### 4. Conjugation of bilirubin

- Conjugation to glucuronic acid (by the enzyme *UDP-glucuronyl transferase*) forming cholebilirubin (Conjugated bilirubin)

### 5. Excretion of bilirubin

- Conjugated bilirubin is excreted into the bile  $\rightarrow$  intestine  $\rightarrow$ 
  - a. Converted\* into stercobilinogen (by the intestinal bacteria)
  - b. Small amount is deconjugated by glucuronidase  $\rightarrow$  Unconjugated bilirubin  $\rightarrow$  EHC
- Stercobilinogen:
  - a. Converted\* (by colon air)  $\rightarrow$  Stercobilin  $\rightarrow$  Stools (brown color)
  - b. Small amount is reabsorbed into the EHC
    - Or  $\rightarrow$  Re-excreted by the liver into the bile
    - $\rightarrow$  Renal excretion as urobilinogen (Converted on standing into urobilin)

Unconjugated bilirubin	Conjugated bilirubin
Hembilirubin	Cholebilirubin
Indirect bilirubin	Direct bilirubin
Bound to albumin	Not bound
Water insoluble	Water soluble
Can't be excreted in urine	Can be excreted in urine



## Etiology of Indirect Hyperbilirubinemia

### A) ↑↑ Production of bilirubin

1. Hemolytic disease of the newborn
  - Rh incompatibility
  - ABO incompatibility
  - Minor groups (Kell, Kidd, Duffy...)
2. Hemolytic anemia
  - Membrane (Hereditary spherocytosis)
  - Enzyme (G-6-PD deficiency)
  - Hb (α-Thalassemia)
3. Polycythemia (IDM, TTTS...)
4. Enclosed hematoma (cephalhematoma, subgaleal hematoma, ICH)
5. Neonatal sepsis
6. ↑↑ Enterohepatic circulation (EHC)
  - CHPS
  - Intestinal obstruction & Hirschsprung disease
  - Inadequate calories
7. Drugs
  - Vitamin K
  - Maternal oxytocin
  - Sulfonamides

### B) ↓↓ Uptake

1. Gilbert's syndrome
2. Breast milk jaundice
3. Hypothyroidism
4. Hypoxia & acidosis

### C) ↓↓ Conjugation

1. Physiologic jaundice
2. Breast milk jaundice
3. Hypothyroidism
4. Crigler-Najjar syndrome

In many neonates with neonatal jaundice, the cause can not be identified

#### Gilbert's Syndrome (AD)

- 2-5% of population
- ↓↓ Uptake & conjugation
- Accidentally discovered
- ↑↑ Bilirubin (Indirect)
- Rx: Reassurance

#### Crigler-Najjar syndrome

1. Type I (Complete enzyme ↓↓)
  - AR
  - 100% kernicterus
2. Type II (Partial enzyme ↓↓)
  - AD
  - Phenobarbitone

## Physiological Jaundice

### Etiology

#### A) ↑↑ Production of bilirubin

- ↑↑ RBCs/Kg
- ↓↓ RBCs life span

#### B) ↓↓ Uptake (Liver immaturity ↓↓ X & Y proteins)

#### C) ↓↓ Conjugation (↓↓ glucuronyl transferase enzyme)

	Physiological Jaundice	Pathological Jaundice
Onset	2 <sup>nd</sup> or 3 <sup>rd</sup> day	Any time (1 <sup>st</sup> 24 hr)
Rate of ↑↑	< 5 mg/Kg/day	> 5 mg/Kg/day
Peak	12 in full-term, 14 in preterm	>12 in full-term, >14 in preterm
Duration	5-7 days in FT, 10-14 in preterm	Longer duration
Conjugated bilirubin	< 20% < 2 mg%	> 20% > 2 mg%

## Approach to a case of Neonatal Jaundice

### A) History

- Onset of jaundice
- Family history (hemolytic anemia, G-6-PD deficiency...)
- Maternal diseases (DM, TORCH...)
- Maternal drugs (Oxytocin, sulfonamides...)
- Perinatal history (asphyxia, cephalhematoma...)
- Nutritional (breastfeeding...)

Jaundice usually starts in the head  
→ abdomen → limbs

Jaundice is difficult to be detected clinically in preterm & dark-colored infants

≤ 24 hr	> 24 hr	Late-onset or prolonged
Hemolytic disease of the NB	Physiological Jaundice	Breast milk jaundice
Hemolytic anemia...	Breast milk jaundice	Hypothyroidism
	Neonatal sepsis	Crigler-Najjar syndrome
	Enclosed hematoma	CHPS
	Crigler-Najjar syndrome	
Cholestasis (TORCH)	Cholestasis (EHBA, Metabolic...)	Cholestasis (EHBA, Metabolic..)

### B) Examination

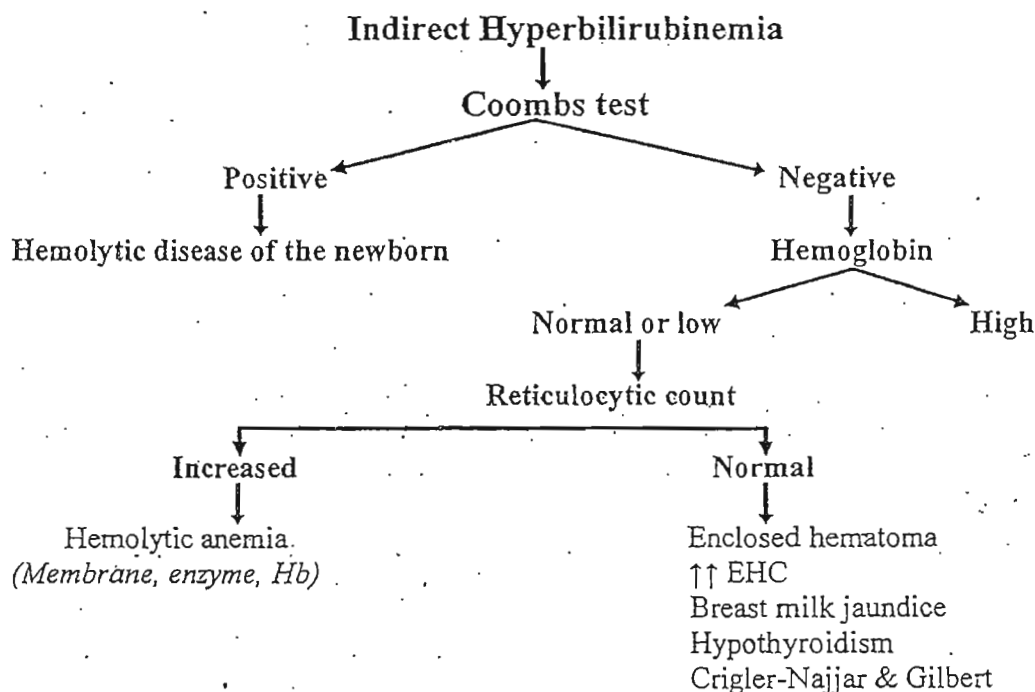
- Gestational age & weight (for treatment plan)
- Color of jaundice (bright yellow or greenish)
- Color of urine & stools (Clay-colored stools in EHBA)
- Manifestations of TORCH (microcephaly, HSM, rash...)
- Manifestations of neonatal sepsis (poor feeding, poor reflexes...)
- Manifestations of Down syndrome?

Causes of NJ in Down syndrome  
1. Annular pancreas  
2. Hypothyroidism (Anti-thyroid Ab)

### C) Investigation

- Laboratory: serum bilirubin (total & direct), CBC, reticulocytic count, coombs test, sepsis screen, thyroid profile, metabolic screen...
- Imaging: Abdominal US for EHBA, organomegaly...
- Invasive: Liver biopsy (In cases of cholestasis)

Transcutaneous bilirubin is useful in screening (= TcB)





## Breast milk associated jaundice

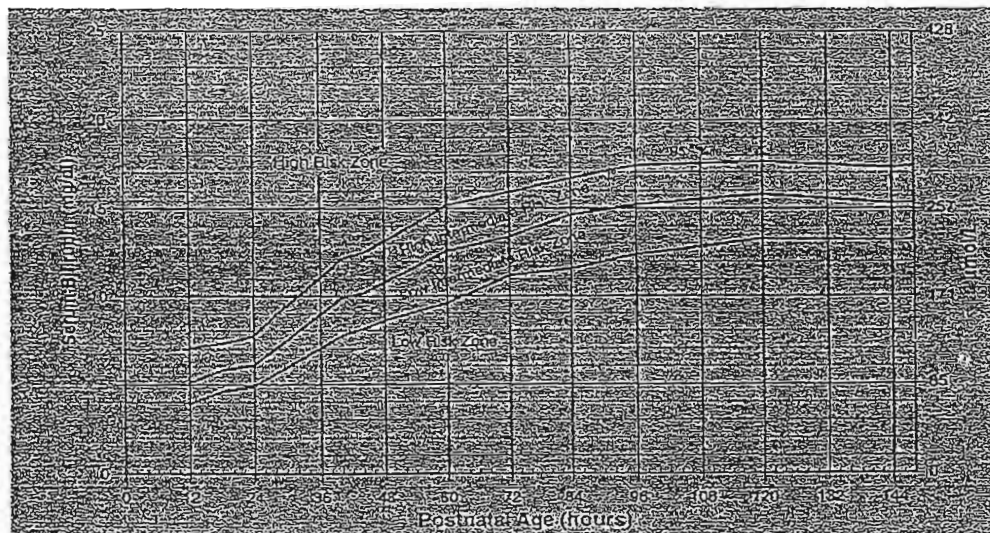
	Breast milk jaundice	Breast feeding jaundice
Incidence	2 %	13 %
Type	Indirect hyperbilirubinemia	Indirect hyperbilirubinemia
Onset	Late-onset > D <sub>7</sub>	1 <sup>st</sup> 3-4 days
Bilirubin Level	10-30 mg%	> 12 mg%
Kernicterus	Has been reported	No
Etiology	1. ↓↓ Conjugation (milk pregnandiol) 2. ↑↑ Milk glucuronidase activity 3. ↑↑ Milk lipoprotein lipase activity → ↑↑ FFA → ↓↓ uptake & conjugation	1. ↓↓ Milk intake & ↓↓ stooling 2. ↓↓ Caloric intake 3. Dehydration
Treatment	▪ Stop breast feeding for 1-2 days ▪ Phototherapy or exchange transfusion	▪ Frequent breast feeding ▪ Avoid Glucose 5% (↓↓ Calories)

## End-tidal carbon monoxide

- Carbon monoxide excretion by the lungs is a by-product of conversion of heme to UCB
- ↑↑ CO is an indicator of ↑↑ production of UCB
- Normal CO excludes hemolysis

## Risk of development of significant hyperbilirubinemia

The risk can be identified by the following nomogram



Nomogram for designation of risk in well newborns at  $\geq 36$  wks & birth weight  $\geq 2000$  g or  $\geq 35$  wk and birth weight  $\geq 2500$  g. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level

## Kernicterus

### (Bilirubin Encephalopathy)

#### Definition

It is neurological syndrome resulting from deposition of unconjugated bilirubin in the brain; basal ganglia & brain stem nuclei

#### Incidence

30% of neonates with untreated hemolytic jaundice with bilirubin level > 25-30 mg%

#### Risk Factors

##### 1. Bilirubin level

There is wide range depending on the weight, gestational age & co-morbid conditions

Suggested maximal UCB concentrations (mg %)

	Uncomplicated course	Complicated course
< 1.000 gm	12	10
1.000-1.250 gm	14	12
1.250-1.500 gm	16	14
1.500-2.000 gm	18	16
2.000-2.500 gm	20	18

Complicated??

Hypoalbuminemia  
Hypoxia  
Hypoglycemia  
Hypothermia  
Hemolysis  
Acidosis  
Meningitis

##### 2. Duration of exposure to hyperbilirubinemia: 2-5 days

##### 3. Factors that ↑↑ free UCB

- Hypoalbuminemia
- Drugs (sulfonamide, rapid infusion of ampicillin...)
- ↑↑ FFA (starvation, hypoglycemia)

##### 4. Factors that ↑↑ permeability of the BBB

- Acidosis
- Asphyxia (hypoxia)
- Prematurity
- Hypothermia
- Hypoglycemia
- Meningitis & seizures

#### Pathology

- a. Gross: Yellow staining of the brain (basal ganglia, thalami, cerebellum & brain stem nuclei)
- b. Microscopic: Gliosis & atrophy of nerve cells & fibers

#### Clinical Picture

##### A) Acute form

- ☑ Phase 1 (1-2 days): Lethargy, poor reflexes, high-pitched cry, seizures, hypotonia
- ☑ Phase 2 (3-7 days): Opisthotonus, bulging AF, seizures, hypertonia
- ☑ Phase 3 (> 1 wk): Few abnormalities, hypertonia (Apparent recovery)

##### B) Chronic form

- ☑ 1<sup>st</sup> year: Opisthotonus, seizures, rigidity
- ☑ 2<sup>nd</sup> year: Choreoathetosis, ↑↑ rigidity, hearing loss
- ☑ 3<sup>rd</sup> year: Choreoathetosis, spastic quadriplegia, hearing loss, mental retardation

#### Prevention

1. Measurement of serum bilirubin in any baby with jaundice at < 24 hrs
2. F/U assessment for jaundice in neonates discharged before 48 hr after birth
3. Universal screening has been recommended
4. Avoid routine supplementation with H<sub>2</sub>O or glucose & encourage breast feeding (↑↑ Calories)
5. Proper Rx of jaundice; Use bilirubin graphs (plot bilirubin level against age in hours)
6. Management plan

# Management of Unconjugated Hyperbilirubinemia

## Introduction

- The need of treatment is known by plotting the bilirubin level on a graph against age in hours
- The absolute level & serial bilirubin measurements identify the need & nature of Rx

## I Treatment of etiological cause

- ☒ Hypothyroidism
- ☒ Breast milk-related jaundice
- ☒ Encourage enteral feeding

## II Phototherapy

### Rationale

Blue-green light (wave length = 425-475 nm) converts UCB to harmless isomers

- Photo-configurational isomerization
- Photo-structural isomerization (*forming lumirubin*)

### Indications

1. ↑↑ UCB according to special graphs
2. Before & in-between exchange transfusions
3. Prophylactic phototherapy in VLBW, hemolytic disease & in cephalhematoma

### Procedure

- Naked except for the eye & ♂ genitalia
- Distance between the baby & the light source should be  $\approx 45$  cm (*most effective*)
- Continuous exposure (can be interrupted by feedings) "Mother-infant bonding"
- Frequent change of position to allow maximal skin exposure
- Monitoring: Temperature every 2 hrs, hydration status & weight (↑↑ daily water requirements by 20%)
- F/U of bilirubin level & removal of phototherapy when low non-toxic level is reached

### Effectiveness of phototherapy

- Light wave length
- Distance
- Skin exposure
- Rate of hemolysis

<p><b>Expected response:</b> 1-3 mg % after 12-24 hrs</p>
---

### Side Effects

1. Hyperthermia
2. Dehydration
3. Skin rash (erythematous macular rash)
4. Hyperthermia
5. Loose stools
6. Bronze baby syndrome (brownish discoloration in cases of conjugated hyperbilirubinemia)
7. Corneal damage
8. DNA damage (mutations in gonads)

- |  |
|--|
| <ul style="list-style-type: none"> <li>▪ Skin color is <u>Not</u> a guide to hyperbilirubinemia</li> <li>▪ Change lamps every 2,000 hr of use</li> <li>▪ Ordinary fluorescent lamps are useless</li> </ul> |
|--|

## III Maximum-Intensive Phototherapy

- ☒ Special blue fluorescent lamps
- ☒ Distance is 15-20 cm from the baby
- ☒ Fiber-optic phototherapy blanket under the infant's back

## IV Exchange Transfusion

### Indications

1. Hemolytic diseases of the NB???
2. Hemolytic anemia
3. Sepsis
4. DIC
5. Polycythemia
6. Respiratory depression by drugs or general anesthesia
7. Hypermagnesemia
8. Inborn errors of metabolism (Maple-syrup urine disease)

### Blood used in Exchange transfusion

Type of blood: Fresh, warm, washed (↓↓ plasma proteins), irradiated (↓↓ GVHD), CMV free

#### Blood group:

- Mother O<sup>-</sup> → O<sup>-</sup> blood
- Mother O<sup>+</sup> → O<sup>-</sup> or O<sup>+</sup> blood
- Any other group → Blood-group of the baby & Rh of the mother

#### Volume

Double blood volume =  $2 \times 85 \times \text{Wt}$

### Procedure

#### A) Assessment

Clinical: Vital signs, weight, gestational age

Lab: Hb%, Hct, bilirubin, reticulocytic count, coombs test, electrolytes, blood glucose, ABG

#### B) Order blood for exchange [start phototherapy, NPO, Glucose 10%]

#### C) Steps

- Aseptic (hand washing, sterile gown, gloves, towels...)
- Radiant warmer
- Umbilical vein cannulation
- Alternating withdrawal of 5-20-cc of infant's blood & infusion of equal volume of donor's blood. Simultaneous (isovolumetric)
- The last 10-20cc are transfused to the baby
- 1 cc Ca gluconate is given every 100 cc transfused blood
- Heparin may be used to maintain patency of the umbilical catheter
- Protamine sulphate should be available
- Glucose 25% if hypoglycemia occurs
- **Monitoring:** Vital signs, blood glucose, Ca, ABG
- **Duration:** 45-60 min

#### D) After exchange

- Phototherapy
- Continue IVF using Glucose 10%
- Antibiotics
- F/U investigation: Bilirubin, CBC, electrolytes, glucose, blood culture

### Complications

1. Complications of umbilical vein catheterization
2. Electrolyte disturbances: ↓↓ Ca, ↓↓ glucose, ↑↑ K, Acidosis
3. Infection: Bacteremia, HBV, HCV, HIV, CMV
4. NEC
5. Hypothermia
6. Arrhythmias
7. Volume overload (Heart failure)
8. Bleeding (Thrombocytopenia & ↓↓ coagulation factors)
9. GVHD
10. Death (1: 100-300)

#### Indications in hemolytic disease of NB

1. Cord blood Hb  $\leq 10$  g%
2. Cord blood Bilirubin  $\geq 5$  mg%
3. Reticulocytes  $\geq 15$  %
4. Serum bilirubin  $> 6$  mg% in the 1<sup>st</sup> 6 hr
5. Serum bilirubin ↑↑ by  $\geq 0.5$ -1 mg%/hr
6. Severe hemolysis in a sibling

## V Phenobarbital

### Actions

- Hepatic microsomal enzyme inducer
- ↑↑ Conjugation

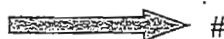
### Uses

- Indirect hyperbilirubinemia
- Direct hyperbilirubinemia (2ry to inspissated bile syndrome)
- Crigler-Najjar syndrome type II (partial enzyme deficiency)

### Side Effects

- Lethargy, ↓↓ cognitive function
- Slow action

## VI Heme Oxygenase Inhibitors (Metalloporphyrins)



### Actions

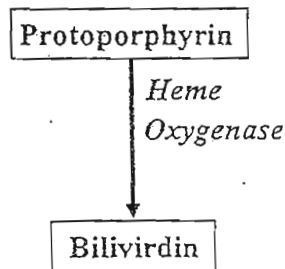
- Inhibition of heme oxygenase
- Still under trials

### Indications

Prophylactic when neonatal jaundice is anticipated (e.g., ABO incompatibility...)

### Example

Tin & Sn mesoporphyrin (IM)



## VII IVIG

### Actions

Saturation of spleen & RES Fc receptors with Ig → ↓↓ RBCs destruction

### Indications

Isoimmune hemolytic disease (Ab mediated destruction of RBCs) when bilirubin approaches exchange levels despite phototherapy

### Dose

0.5-1 g /Kg/dose every 12 hr

# Physiologic Anemia of Infancy

## Introduction

- In utero, oxygen saturation is low (45%) → Erythropoietin level is high
- Term: Cord blood Hb% = 14-20 g %
- VLBW: Cord blood Hb% = 12-18 g %
- After birth, oxygen saturation is (95%) → Erythropoietin level is low

## Etiology

1. ↓↓ Erythropoiesis (↓↓ Erythropoietin)
2. ↓↓ RBCs life span
3. ↑↑ Blood volume
4. ↑↑ Nutritional requirements
5. Dietary deficiencies
  - Vitamin E (especially with iron supplementation)
  - Folic acid.

Iron therapy in neonates with ↓↓ Vitamin E → Hemolytic anemia + Edema + Thrombocytosis

## Anemia of prematurity

- It is exaggeration of physiologic anemia
- Preterm neonates have the same (but exaggerated risk factors; *mention*)

## Level (*Nadir is the lowest Hb level*)

	Time of nadir (± 3 wk)	Hb% at nadir (± 1 g %)
Term	9	10
Preterm	7	8

## Clinical Picture

- Physiological anemia is not a functional anemia (adequate O<sub>2</sub> delivery to the tissue)
- Anemia of prematurity: pallor, tachycardia, tachypnea, poor weight gain, apnea

## Prevention

- Vitamin E (15-25 IU/ day)
- Iron supplementation (2-4 mg/Kg/day) should be given once full enteral intake is given
- Folic acid (*routine in some centers*)
- Breast milk (↓↓ linoleic) should be used to maintain ↓↓ PUFA in RBCs membranes
- Recombinant human erythropoietin [r-HuEPO]: 200-250 units/kg SC (3 times/ wk) *can* be used to prevent anemia of prematurity. Supplementation with iron & vitamin E is indicated
- ↓↓ Blood samples

## Treatment

- ☒ Asymptomatic: Only F/U. No treatment except if Hb ≤ 7 g %
- ☒ Symptomatic: Blood transfusion. The decision of transfusion depends on:
  - Hb level
  - Severity of symptoms
  - Co-morbid conditions (mechanical ventilation, BPD, CHD)

Routine use of rH-EPO is not recommended

# Pathological Anemia in the Newborn

## Etiology

### A) Blood loss

1. Before birth
  - Feto-maternal transfusion
  - TTTS
2. During delivery
  - Placenta: placenta previa, accidental hemorrhage, incision
  - Cord: Velamentous insertion, vasa previa, rupture
3. Neonatal bleeding
  - Head
    - Cranial: Cephalhematoma, subgaleal hematoma
    - Intracranial: ICH
  - Internal organs

Congenital pure red cell aplasia  
= Diamond-Blackfan syndrome

### B) ↓↓ Production

1. ↓↓ Precursors
  - Pure red cell aplasia (congenital or acquired "Parvo B<sub>19</sub>")
  - Constitutional aplastic anemia (Fanconi anemia)
  - Osteopetrosis
  - Congenital leukemia
2. Normal precursors
  - Congenital Dyserythropoietic anemia
3. Specific factors
  - Folic acid, B<sub>12</sub>, Iron
  - Proteins, Cu

### C) ↑↑ Destruction

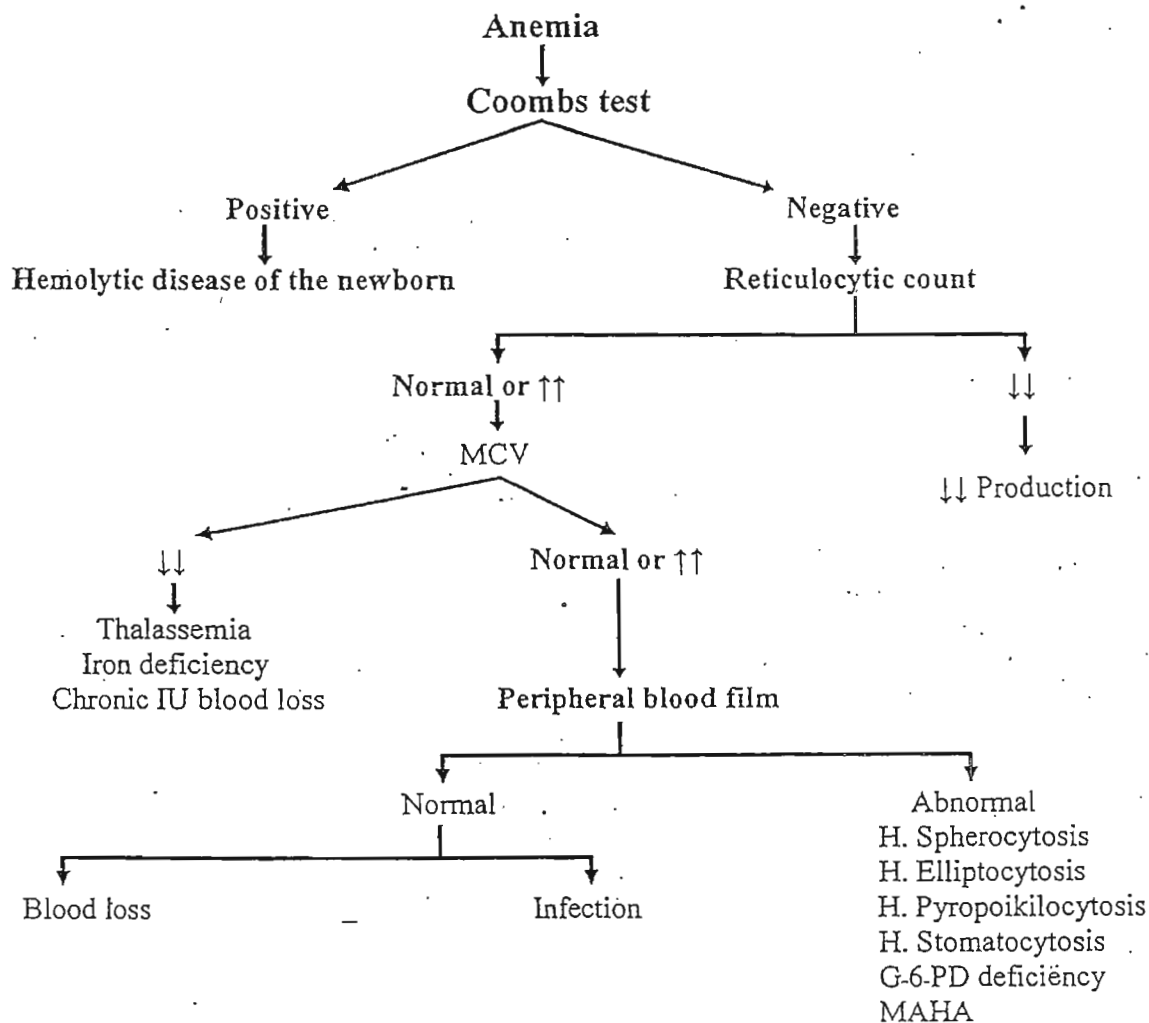
1. Intra-corpuscular
  - Membrane (Hereditary spherocytosis)
  - Enzyme (G-6-PD deficiency)
  - Hb (α-Thalassemia)
2. Extra-corpuscular
  - Immune-mediated
    - Rh, ABO, Minor groups ...
    - Maternal autoimmune diseases (SLE)
    - Drug-induced (penicillins, valproate...)
  - Non-immune
    - MAHA (Renal vein thrombosis, DIC...)
    - Infection (sepsis)
    - Vitamin E deficiency

## Clinical Picture

- Pallor, tachycardia, tachypnea, poor weight gain, apnea
- Anemic heart failure

Diagnostic Approach (= History + examination + investigation). See diagram

Prevention (as in physiologic anemia + Rx of the cause)



**Prevention** (as in physiologic anemia + Rx of the cause)

### Treatment

#### A) Blood transfusion

Type of blood:

- Fresh
- Warm
- Filtered (Leukocyte depleted)
- Washed (↓↓ plasma proteins)
- Irradiated (↓↓ lymphocytes)
- CMV free

Volume

10-20 cc/Kg (Smaller volumes should be used with anemic HF)

Indications

1. Hemolytic disease of the newborn & hemolytic anemia
2. Hb < 10-12 g % in neonates with RD to ↑↑ oxygenation
3. Anemic HF
4. Sick preterm (sepsis, pneumonia, BPD)
5. Preterm neonates with apnea & bradycardia
6. Preterm neonates with poor weight gain
7. Asymptomatic infants with Hb < 7 g % & reticulopenia

#### Packed or whole blood

Whole blood in exchange & blood loss  
Packed RBCs in other indications

#### B) r-HuEPO (as before)



# Polycythemia

## Definition

Polycythemia is venous blood hematocrit (Hct) > 65% [or Hb ≥ 21 g%]

Plethora is deep red appearance "*Clinical sign*"

## Incidence

It is ↑↑ in SGA, post-term babies & at high altitudes (↓↓ O<sub>2</sub>)

## Etiology

A) Intrauterine Hypoxia-IUGR (↑↑ Erythropoietin)

B) ↑↑ Blood volume

- Materno-fetal transfusion
- TTTS
- Placental transfusion (delayed cord clamping or holding the baby below the mother)

C) Other causes

- IDM, LGA & Beckwith-Wiedmann syndrome
- Trisomies 21, 13, 18
- Throtoxicosis & 7 hypothyroidism

## Clinical Picture

- ☒ Asymptomatic
- ☒ Facies: Plethora
- ☒ CNS: lethargy, seizures, stroke
- ☒ CVS: Heart failure
- ☒ Respiratory system: RD or apnea
- ☒ GIT: Feeding difficulties & ↑↑ risk of NEC
- ☒ Metabolic: hypoglycemia, hypocalcemia, hyperbilirubinemia



## Investigations

- Hct
- Blood viscosity (viscometer)

## Prevention

- Antepartum management of placental insufficiency...
- Intrapartum: avoid *milking* of the cord, avoid holding the baby below the placenta

## Treatment

☒ Symptomatic: Partial exchange transfusion using fresh plasma or normal saline

$$\text{Volume of exchange} = \text{Blood volume} \times \frac{\text{Observed Hct} - \text{Desired Hct}}{\text{Observed Hct}}$$

Complications: Complication of vascular access (umbilical venous catheter)

☒ Asymptomatic:

- a. Hct = 65-70% → Close observation + IV fluids
- b. Hct > 70% → Partial exchange transfusion

## Prognosis

- ↓↓ IQ
- Speech deficits & learning difficulties
- Complications of umbilical venous catheter (e.g., portal hypertension...)

# Hemolytic Disease of the Newborn

## (Erythroblastosis Fetalis)

### Definition

Transplacental passage of maternal antibodies causing hemolysis of the fetal RBCs  
It is caused by Rh, ABO or minor group incompatibility (Kell, Kidd, Duffy...)

## Rh Incompatibility

Anti-D Abs occur with:  
1. Blood transfusion  
2. Pregnancy: abortion or delivery

### Introduction

- The Rh system is controlled by 3 pairs of alleles, the most important is D & d alleles
- D allele is dominant over d (DD & Dd are Rh positive)
- Other alleles are C, c, E, e
- Antibodies against Rh system (*Anti-D Antibodies*) are Not naturally occurring & of IgG type

### Pathogenesis

- If the mother is Rh negative & the father is Rh positive, the baby may be Rh positive
- Minute amounts of fetal RBCs pass to the maternal circulation during abortion or delivery causing maternal sensitization (formation of Anti-D Antibodies)
- In subsequent pregnancies, maternal anti-D antibodies cross the placenta, reacting with fetal RBC, causing hemolysis
- These events can occur in the 1<sup>st</sup> pregnancy if the mother was previously sensitized
- Fetal hemolytic anemia (anemia, HF, extramedullary hematopoiesis, bilirubin is not ↑↑)??

### Incidence

Only 5% of babies borne to Rh-negative mothers develop hemolytic disease. Why?

1. The father may be heterozygous
2. Feto-maternal transfusion occurs in only 50% of pregnancies
3. Variable D antigenicity
4. Variable maternal antibody response
5. Concomitant occurrence of ABO incompatibility (↓↓ maternal sensitization)

### Clinical Picture (spectrum with variable severity)

1. **Hemolytic anemia:** pallor, tachycardia, tachypnea
2. **Anemic heart failure:** generalized edema, hepatomegaly, pleural & pericardial effusion
3. **Hydrops**
4. **HSM:** extramedullary hematopoiesis
5. **Hepatic dysfunction:** ↓↓ Albumin
6. **Portal hypertension:**
7. **Ascites**
8. **Hemolytic jaundice:** Unconjugated hyperbilirubinemia is evident within the 1<sup>st</sup> day
9. **Kernicterus:** D<sub>2</sub>-D<sub>5</sub>
10. **RD:** pulmonary congestion, pulmonary edema or pleural effusion
11. **Thrombocytopenia:** 2ry to BM inhibition or DIC
12. **Hypoglycemia:** 2ry to pancreatic cell hyperplasia → hyperinsulinism

### Prevention

1. **Avoid exposure of ♀ to Rh +ve blood**
2. **Anti-D antibodies:** [1 cc = 300 µg]
  - Given IM to the mother within 48-72 hr of placental separation (abortion, labor...)
  - More effective if given at 28-32 wks and at birth

## Diagnosis

### A) Antenatal diagnosis

The mother at risk:

- Rh-negative with the father is Rh-positive
- History of blood transfusion, pregnancy or abortion
- History of previously affected infant

#### 1. Maternal serum titer of IgG anti-D antibodies

- ☒ Done at 12-16 wk, 28-32 wk & at 36 wk
- ☒ Titer  $\geq 1:16$  should be further investigated (Severe if titer  $\geq 1:64$  or rising titer)

#### 2. Fetal U/S (real time & Doppler)

- ☒ Hydrops: pleural, pericardial effusion, ascites, skin edema, HSM
- ☒ Biophysical profile & Doppler
- ☒ Amniocentesis

#### 3. Amniocentesis

- ☒ Done at 18-20 wk & at 1-2 wk intervals if titer  $\geq 1:16$  or positive US
- ☒ Measurement of UCB in the amniotic fluid by spectrophotometry
- ☒ The risk is categorized by 3 zones
  - Zone 1: Mild disease
  - Zone 2: Moderate disease
  - Zone 3: Severe disease (impending fetal death)

Change in the optical density

#### 4. PUBS (Percutaneous umbilical blood sampling)

- ☒ Done if the OD deviation is in zone 3
- ☒ Measurement of Hb & Hct
- ☒ Blood transfusion is indicated if Hct  $< 25\%$

### B) Postnatal diagnosis

- ☒ Coombs: positive
- ☒ Hb & Hct:  $\downarrow\downarrow$
- ☒ Bilirubin:  $\uparrow\uparrow$
- ☒ Reticulocytic count:  $\uparrow\uparrow$

Any NB born to Rh-negative mother:  
 • ABO-Rh  
 • Hb, Hct  
 • Coombs test

## Treatment

### A) Antenatal [Aim = prevention of hydrops]

#### 1. Induction of labor

- If  $\geq 33$  wk + zone 2 or 3 OD deviation
- Risk of prematurity should be considered

#### 2. IU intraumbilical blood transfusion

- Fresh, irradiated, group O, Rh negative blood (cross-matched to maternal serum)
- Risk of the procedure & GVHD

### B) Postnatal [Aim = prevention of kernicterus]

1. Stabilization: Respiratory support, packed RBCS, correction of acidosis
2. Exchange transfusion. When?
3. Phototherapy
4. IVIG
5. Metalloporphyrin

## DD

Other causes of hydrops

## Hydrops Fetalis

### Definition

It is excessive abnormal accumulation of fluid in  $\geq 2$  fetal compartments  
[Peritoneum, pericardium, pleura, placenta, amniotic fluid, skin]

### Etiology

1. Immune hydrops: Rh incompatibility
2. Idiopathic
3. Anemia: All causes of pathological anemia of the newborn can cause hydrops
4. CVS
  - Arrhythmias: SVT, congenital heart block
  - Structural: HLHS, complete AV canal, cardiomyopathy
  - Vascular: cerebral AV malformation (aneurysm of vein of Galen)  
Klippel-Trenaunay syndrome  
Chorioangioma of the cord or placenta
  - Lymphatics: Turner, Noonan, cystic hygroma, lymphangiectasia (chylous ascites...)
5. CNS: encephalocele, myotonic dystrophy
6. Lungs: congenital diaphragmatic hernia, cystic adenomatoid malformation
7. Renal: congenital nephrosis
8. GIT: Intestinal obstruction
9. Tumours: Neuroblastoma, hepatoblastoma, teratomas
10. Metabolic: Gaucher, Niemann-Pick, MPS
11. Chromosomal: Trisomies 21, 13, 18
12. Bone disease: Osteogenesis imperfecta, skeletal dysplasia
13. Congenital infection: TORCH, Parvovirus B<sub>19</sub>
14. IDM

### C/P Investigation Treatment

## ABO Incompatibility

### Introduction

- Antibodies (agglutinins) against ABO system are naturally occurring & of IgM type
- Sometimes antibodies are of IgG type that can cross the placenta, reacting with fetal RBCs, causing hemolysis

### Pathogenesis

- If the mother is group O & the fetus is group A, B or AB
- Maternal anti-A & anti-B antibodies cross the placenta, causing fetal RBCs hemolysis
- It may occur in the 1<sup>st</sup> born infant

### Incidence

Only 10% of babies borne to group O mothers develop hemolytic disease. Why?

1. Antibodies are usually of IgM type
2. ABO antigenicity is usually low

### Clinical Picture

- Unconjugated hyperbilirubinemia may be evident within the 1<sup>st</sup> day
- Hydrops, kernicterus are rare

### Investigations (as postnatal diagnosis of Rh incompatibility)

### Treatment (as postnatal Rx of Rh incompatibility)

# Hemorrhagic Disease of the Newborn

## Action of Vitamin K

- Carboxylation of coagulation factors
- Carboxylation of glutamic acid in the developing cartilages

## Definition

Transient deficiency of vitamin K dependent coagulation factors (II, VII, IX, X)

## Predisposing Factors

1. ↓↓ Store (more in preterm)
2. ↓↓ Intake (breast milk is poor in vitamin K)
3. ↓↓ Synthesis (↓↓ intestinal flora)
4. Liver immaturity
5. Broad-spectrum antibiotics
6. Malabsorption (fat-soluble vitamin)
7. Maternal drugs (Phenobarbitone, phenytoin, warfarin)

## Clinical Picture

	Early-onset	Classic disease	Late-onset
Onset	1 <sup>st</sup> 24 hr	D <sub>2</sub> -D <sub>7</sub>	1-6 months
Incidence	Very rare	2 %	Variable
Site	<ul style="list-style-type: none"> <li>▪ Cephalhematoma</li> <li>▪ Subgaleal hematoma</li> <li>▪ ICH</li> <li>▪ GIT</li> </ul>	<ul style="list-style-type: none"> <li>▪ GIT</li> <li>▪ Nose, ear, mucosal</li> <li>▪ Circumcision</li> <li>▪ Injection sites</li> </ul>	<ul style="list-style-type: none"> <li>▪ ICH</li> <li>▪ GIT</li> <li>▪ Nose, ear, mucosal</li> <li>▪ Injection sites</li> </ul>
Etiology	Maternal drugs	Vitamin K deficiency	Malabsorption
Prevention	<ul style="list-style-type: none"> <li>▪ Avoid high risk drugs</li> <li>▪ Vit K to mother &amp; baby</li> </ul>	Vit K 0.5-1 mg IM (or several oral doses)	IM or oral vit K supplementation

## Investigations

- ☑ ↑↑ PT, ↑↑ PTT
- ☑ Bleeding time, platelet number & function: Normal
- ☑ PIVKA (= protein induced in vit K absence): ↑↑

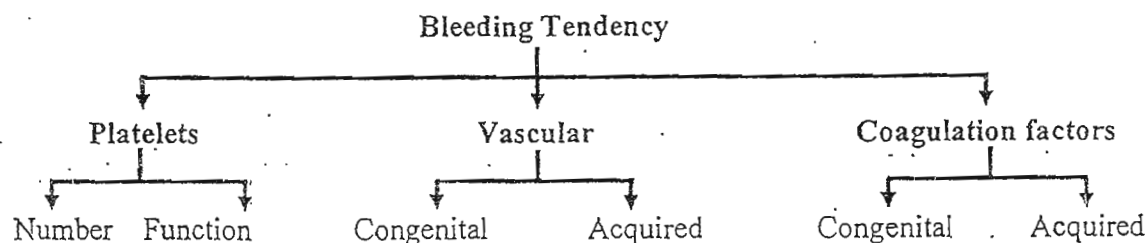
**Apt test:**  
Test done in GIT bleeding to detect maternal RBCs

**Kleihauer test:**  
Test on maternal blood to detect fetal RBCs

## Treatment

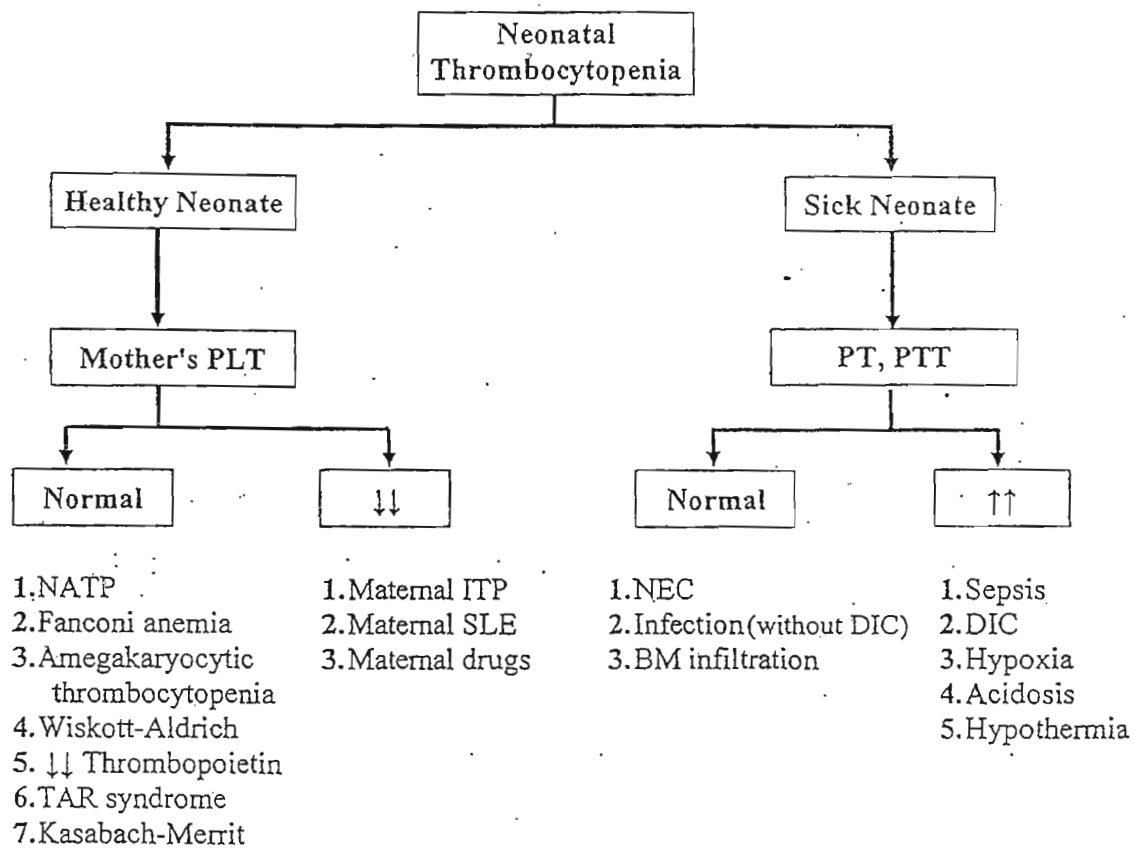
- ☑ Vitamin K (Konakion): 1-5 mg IV
- ☑ Fresh frozen plasma: 10 cc/Kg in cases of serious bleeding
- ☑ Whole blood transfusion: in cases of marked hemorrhage

## Differential Diagnosis [Bleeding tendency in neonates]



# Neonatal Thrombocytopenia

## Etiology



# Retinopathy of Prematurity

## Definition

It is a disease of the immature, incompletely vascularized retina in premature infants treated with O<sub>2</sub> at high concentration

## Incidence

- 65% of preterm neonates < 1.250 g
- 80% of preterm neonates < 1.000 g
- 10% of causes of visual impairment in developed countries

VEGF =  
Vascular endothelial growth factor

## Risk Factors

1. Prematurity\*\*
2. Low birth weight\*\*
3. Hyperoxia & hypoxia
4. Hypercapnia & hypocapnia
5. Acidosis & alkalosis
6. Mechanical ventilation
7. BPD
8. Vitamin E deficiency
9. Sepsis
10. Intra-ventricular hemorrhage

## Pathogenesis

- ☒ ↑↑ O<sub>2</sub> → Retinal VC → Vascular endothelial growth factors (VEGF) → Inappropriate & excessive growth of retinal vessels → BV invade the vitreous body → Vitreous hemorrhage → Fibrosis → Retinal detachment
- ☒ Developmental retinal arrest

## Screening

	USA	UK
Who??	< 1.500 g < 29 wk	< 1.500 g < 32 wk
When??	4-6 wk chronological age 31-32 wk PCA	6-7 wk chronological age
Follow-up	Until regression of retinopathy Or until 36 wk PCA (if no disease)	

## Stages

	Description	Treatment
Stage 1	Flat demarcation line between normally vascularized & non-vascularized retina	No Rx (F/U) Spontaneous resolution
Stage 2	Ridge demarcation...	
Stage 3	New blood vessels ± Vitreous hemorrhage	Cryotherapy Laser photocoagulation
Stage 4	Partial RD	
Stage 5	Complete RD	Retinal Reattachment
Plus disease	Active progressive disease	
		Laser photocoagulation

## Prevention

1. Prevention of prematurity
2. Keep O<sub>2</sub> tension between (50-70 mmHg)
3. Use the least possible FiO<sub>2</sub> for the least possible duration
4. Vitamin E supplementation
5. Anti-oxidants

The risk of hypoxic brain damage should be balanced against the risk of blindness from too much O<sub>2</sub>

# Osteopenia of Prematurity

(Metabolic bone disease of prematurity)

## Definition

It is defective bone mineralization affecting premature infants

## Incidence

30% of VLBW

## Etiology

### A) $\downarrow\downarrow$ Ca & $\downarrow\downarrow$ $\text{PO}_4^*$

1. Dietary deficiency (unsupplemented breast milk, term formula for preterm infants...)
2. Loss of  $\text{PO}_4$  in urine (Fanconi syndrome)
3. Loss of Ca in urine (furosemide therapy)
4. TPN

### B) Vitamin D Deficiency

1. Maternal Vitamin D deficiency
2.  $\downarrow\downarrow$  Intake
3.  $\downarrow\downarrow$  Absorption
4.  $\downarrow\downarrow$  Activation
  - ☒ Hepatic
  - ☒ Renal
5. Type 1 vitamin D dependent rickets
6. Type 2 vitamin D dependent rickets
7. Anticonvulsant therapy (phenytoin, phenobarbitone)

## Clinical Picture

- Deformities
- Pathologic fractures
- Rickets-like (wide AF, frontal bossing, enlarged ends of long bones, rosary beads...)
- Hypotonia

## Investigations

- Ca: Normal or  $\downarrow\downarrow$
- $\text{PO}_4$ :  $\downarrow\downarrow$
- Alkaline phosphate:  $\uparrow\uparrow$
- X-ray: broadening, cupping, fraying,  $\downarrow\downarrow$  bone density,
- Densitometry

## Prevention

- Prevention of prematurity
- Proper maternal nutrition (Ca, vitamin D)
- Dietary management: fortified breast milk or LBW formula for preterm infants

## Treatment

- Vitamin D (400-1.000 IU/day)
- Calcitriol: in cases of defects of vitamin D metabolism (hepatic or renal)
- Ca supplementation
- Treatment of fractures



## Hypomagnesemia

Mg = 1.5 - 2.6 mg%

### Definition

Serum Mg < 1.5 mg. Clinical manifestation occur when Mg < 1.2 mg%

### Etiology

1. Idiopathic with hypocalcemia
2. IDM
3. Iatrogenic: exchange transfusion, TPN
4. Malabsorption (generalized or specific)
5. ↑↑ Renal excretion (Hereditary AD, drugs; aminoglycosides, amphotericin B)

### Clinical Picture

- As hypocalcemia (tetany & convulsions)

↑↑ Mg should be considered in any case of tetany not responding to IV Ca

### Treatment

- IV Magnesium sulphate 10%: slowly (1 cc/Kg)
- Oral maintenance therapy

## Hypermagnesemia

### Definition

Serum Mg > 2.6 mg. Clinical manifestation occur when Mg > 5 mg%

### Etiology

1. Maternal MgSO<sub>4</sub> (Rx of eclampsia)
2. MgSO<sub>4</sub> enema
3. Mg-containing antacids
4. TPN (↑↑ Mg)

### Clinical Picture

- Lower levels: Lethargy, hypotonia, hyporeflexia, hypotension,
- High levels: CNS depression & paralysis (mechanical ventilation may be needed)

### Treatment

- Removal of the source of Mg
- Respiratory support may be needed
- IV Calcium gluconate 10%: slowly (1 cc/Kg)
- Diuretics
- Exchange transfusion

## Hypocalcemia

## Hypercalcemia

# Hypothermia

Estimated heat loss in neonates is 4 times that of an adult.  
Preterm NB is at a greater risk

## Definition

It is body temperature  $\leq 35^{\circ}\text{C}$

## Premature neonates are at risk due to

1. Skin: thin with  $\uparrow\uparrow$  permeability
2. Skin:  $\uparrow\uparrow$  surface area
3. Skin:  $\downarrow\downarrow$  SC fat
4. Not able to curl-up
5. Brown fat:  $\downarrow\downarrow$  FA oxidation
6. Caloric intake:  $\downarrow\downarrow$
7. Activity:  $\downarrow\downarrow$
8.  $\text{O}_2$  consumption:  $\downarrow\downarrow$  (respiratory problems; RDS...)
9. No shivering (till 2 weeks of age).

## Mechanism of heat loss

	How is heat lost	How to avoid
Convection	Heat loss from the skin to the moving cooler air	<ul style="list-style-type: none"> <li>▪ Clothing</li> <li>▪ Boots &amp; hats</li> <li>▪ <math>\uparrow\uparrow</math> Room air Temperature</li> <li>▪ Avoid drafts</li> </ul>
Radiation	Heat loss from the skin to cooler objects in the environment	<ul style="list-style-type: none"> <li>▪ Double-walled incubators</li> </ul>
Evaporation	Heat loss from moist skin & lungs (with $\text{H}_2\text{O}$ )	<ul style="list-style-type: none"> <li>▪ Dryness (immediately after birth)</li> <li>▪ Wrapping (warm towels)</li> <li>▪ <math>\uparrow\uparrow</math> Room air Humidity</li> <li>▪ Use of warm humidified air/<math>\text{O}_2</math></li> </ul>
Conduction	Heat loss from the skin to cooler surfaces in contact with the baby	<ul style="list-style-type: none"> <li>▪ Heated mattresses</li> </ul>

## Clinical Picture

- ☑ Temperature  $\leq 35^{\circ}\text{C}$
- ☑ Facies: Facial erythema, rhinitis
- ☑ Edema & local hardening
- ☑ CNS: Coma
- ☑ CVS: Bradycardia & hypotension
- ☑ Respiratory system: apnea & pulmonary hemorrhage
- ☑ GIT: Feeding difficulties &  $\uparrow\uparrow$  risk of NEC
- ☑ Metabolic: hypoglycemia, acidosis
- ☑ Blood: thrombocytopenia, DIC

Do not allow the newborn to get cold.

### Hypothermia:

- Acidosis
- Hypoglycemia

## Prevention

- Any neonatal examination should be done under radiant warmers
- Incubator care & radiant warmer

## Treatment

- Warming
- Correction of metabolic disturbances (hypoglycemia, acidosis)

## Prognosis

- Mortality = 10%
- Brain damage in 10% of survivors

## Hypoglycemia

Normal neonates produce 4-5 mg/Kg/minute of glucose to maintain glucose homeostasis

### Definition (differs according to the age)

- 1-3 hours: blood glucose level < 35 mg%
- 3-24 hours: blood glucose level < 40 mg%
- After 24 hours: blood glucose level < 45 mg%

### Incidence

1-3: 1000 live births

### Etiology

#### A) Hyperinsulinism

1. IDM, LGA & Beckwith-Wiedmann syndrome
2. Erythroblastosis Fetalis (pancreatic cell hyperplasia)
3. Hyperinsulinemic hypoglycemia of infancy (HHI): previously called "nesidioblastosis"
4. Maternal drugs: Sympathomimetics (tocolytics), thiazides, large glucose infusion

#### B) ↓↓ Glycogen stores

1. Prematurity
2. SGA (IUGR)
3. ↓↓ Intake

#### C) ↑↑ Requirements

1. RDS, HF, hypothermia
2. Polycythemia

#### D) ↓↓ Production

1. HIE
2. Maternal β-blockers (propranolol)
3. Defects in Carbohydrates metabolism
  - Glycogen storage disease
  - Galactosemia
  - Hereditary fructose intolerance (↓↓ Aldolase B)
4. Defects in Fat metabolism
  - FA oxidation defects (hypoketotic hypoglycemia)
5. Defects in Protein metabolism
  - Tyrosinemia
  - Maple syrup urine disease
  - Propionic academia
6. Endocrinal causes
  - Congenital hypopituitarism
  - Adrenal insufficiency

#### E) Iatrogenic

1. Exchange transfusion
2. Sudden cessation of IVF or TPN

#### Persistent Hypoglycemia

1. HHI
2. Metabolic
3. Endocrinal

### Clinical Picture

A) ↑↑ Catecholamines: Tachycardia, palpitation, pallor, sweating, tremors

B) Cerebral glucopenia: Headache, hunger, drowsiness, confusion, coma, convulsions

### Investigations

- Serial blood glucose monitoring every 1 hr (for 6-8 hrs) till readings > 40 mg%
- Investigations of the cause (e.g., reducing substance in urine, hormonal assay...)

## Treatment

- A) At-risk asymptomatic neonates with normal blood glucose (IDM, LGA, SGA...)
- ☒ Close monitoring of blood glucose
  - ☒ Early oral or Ryle feeding
  - ☒ IVF can be used if there is no response (after 2 hrs) or if there is CI of enteral feeding
  - ☒ IDM < 2 Kg should start IVF (↓↓ Glycogen stores): 4-5 mg/Kg/minute
- B) Asymptomatic hypoglycemia
- ☒ IV glucose 10% (2 cc/Kg)
  - ☒ Followed by continuous infusion at 4-5 mg/Kg/minute
- C) Symptomatic hypoglycemia (No seizures)
- ☒ IV glucose 10% (2 cc/Kg)
  - ☒ Followed by continuous infusion at 8 mg/Kg/min
- D) Symptomatic hypoglycemia (Seizures)
- ☒ IV glucose 10% (4 cc/Kg)
  - ☒ Followed by continuous infusion at 8 mg/Kg/min
- E) Persistent hypoglycemia
- ☒ Glucose infusion rate 10-12 mg/Kg/min
  - ☒ Glucose concentration can be ↑↑ up to 12% (peripheral line) or 20% (Central line)
- F) After stabilization
- ☒ Gradual tapering of IV glucose
  - ☒ Gradual advancement of oral feedings
- G) Other lines of management (resistant cases; HHI)
- ☒ Hydrocortisone (2.5 mg/Kg/12 hr)
  - ☒ Diazoxide
  - ☒ Octreotide
  - ☒ Glucagon
  - ☒ Subtotal pancreatectomy (HHI)

$$\text{GIR} = \frac{\text{Fluid rate (cc/hr)} \times \text{Glucose Conc. \%}}{6 \times \text{Body weight}}$$

## Prognosis

- ☒ Good in properly treated infants
- ☒ Neurological sequelae occur with prolonged hypoglycemia (CP)
- ☒ Primary etiology

## NB: White classification

Class	Comment
Gestational Diabetes	Diabetes not known before pregnancy
GD diet	Diabetes controlled by diet only
GD insulin	Requires insulin
Class A	Prediabetes (History of large babies > 4 Kg)
Class B	Onset > 20 yrs of age
Class C	Onset at 10-19 yrs of age
Class D	Onset < 10 yrs of age
Class F	Nephropathy
Class R	Retinopathy
Class RF	Both
Class G	Many reproductive failures
Class H	Heart disease
Class T	Prior renal transplantation

## Treatment

### A) At-risk asymptomatic neonates (IDM, LGA, SGA...)

- ☒ Close monitoring of blood glucose
- ☒ Early oral or ryle feeding
- ☒ IVF can be used if there is no response or if there is CI of enteral feeding

### B) Asymptomatic hypoglycemia

- ☒ IV glucose 10% (2 cc/Kg)
- ☒ Followed by continuous infusion at 4-5 mg/Kg/minute

### C) Symptomatic hypoglycemia (No seizures)

- ☒ IV glucose 10% (2 cc/Kg)
- ☒ Followed by continuous infusion at 8 mg/Kg/min

$\text{GIR} = \frac{\text{Fluid rate (cc/hr)} \times \text{Glucose Conc. \%}}{6 \times \text{Body weight}}$
---

### D) Symptomatic hypoglycemia (seizures)

- ☒ IV glucose 10% (4 cc/Kg)
- ☒ Followed by continuous infusion at 8 mg/Kg/min

### E) Persistent hypoglycemia

- ☒ Glucose infusion rate 10-12 mg/Kg/min
- ☒ Glucose concentration can be ↑↑ up to 12% (peripheral line) or 20% (central line)

### F) After stabilization

- ☒ Gradual tapering of IV glucose
- ☒ Gradual advancement of oral feedings

### G) Other lines of management (resistant cases; HHI)

- ☒ Hydrocortisone (2.5 mg/Kg/12 hr)
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## Prognosis

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- ☒ Primary etiology

## Infant of Diabetic Mother

### Introduction

#### A) Effects of pregnancy on maternal DM "Diabetogenic"

- Alimentary glucosuria
- Renal glucosuria
- Production of anti-insulin: estrogen, progesterone, cortisol, placental insulinase enzyme, human placental lactogen (hPL)

#### B) Effects of DM on pregnancy (mother & fetus)

- |   |                         |
|---|-------------------------|
| • Abortion                                  | • Obstructed labor      |
| • IUFD                                      | • Birth injury          |
| • Prematurity                               | • Neonatal hypoglycemia |
| • Pregnancy-induced hypertension (PIH)      | • Neonatal hypocalcemia |
| • Polyhydramnios                            | • RDS                   |
| • Congenital anomalies (cardiac, sacral...) | • Polycythemia          |
| • Macrosomia                                | • Neonatal jaundice     |

# Infant of Diabetic Mother

## Introduction

### A) Effects of pregnancy on maternal DM "Diabetogenic"

- Alimentary glucosuria
- Renal glucosuria
- Production of anti-insulin: estrogen, progesterone, cortisol, placental insulinase enzyme, human placental lactogen (hPL)

### B) Effects of DM on pregnancy (mother & fetus)

- Abortion
- IUFD
- Prematurity
- Pregnancy-induced hypertension (PIH)
- Polyhydramnios
- Congenital anomalies (cardiac\*, sacral\*...)
- Macrosomia
- Obstructed labor
- Birth injury
- Neonatal hypoglycemia
- Neonatal hypocalcemia & hypomagnesemia
- RDS
- Polycythemia
- Neonatal jaundice

## Pathophysiology

Maternal hypoglycemia, fetal hyperinsulinemia

- ☑ Maternal hyperglycemia → Fetal hyperglycemia → pancreatic cell hyperplasia → Fetal hyperinsulinemia → ↑↑ Uptake & utilization (3) of glucose → Macrosomia
- ☑ Placental separation → ↓↓ glucose delivery to the fetus.
- ☑ Hyperinsulinemia → Neonatal hypoglycemia
- ☑ Hyperinsulinemia → Surfactant deficiency (RDS)

## Clinical Picture

### Causes of LBW in IDM:

1. Preterm delivery
2. Placental insufficiency

1. Birth weight: macrosomia
2. Plethora
3. Neonatal hypoglycemia (25-50%)
4. Neonatal hypocalcemia: tetany & convulsions
5. Polycythemia (30%): due to hyperinsulinemia (↑↑ Erythropoietin) & fetal hypoxia
6. Neonatal jaundice: due to polycythemia, prematurity & glycosylation of RBC membrane
7. Cardiomegaly (30%) & HF: due to ventricular septal hypertrophy "HCM"
8. RD:
  - Cardiac lesions (Heart failure)
  - Respiratory: TTN, RDS, pneumonia
  - Polycythemia
  - Hypoglycemia
  - PPHN: (↓↓ Glucose, ↓↓ Ca, HF, Polycythemia)
9. Congenital anomalies:
  - Cardiac: Ventricular septal hypertrophy, VSD, ASD, TGA
  - Sacral agenesis
  - Renal: dysplasia
  - GIT: small left colon syndrome
  - CNS: anencephaly, meningocele
10. Renal vein thrombosis

## White classification

It is used to estimate prognosis and perinatal outcome; Complications are:

- ☑ Minimal in infants of mothers with gestational diabetes
- ☑ High in infants of diabetic mothers with renal, cardiac, or retinal disease

## Investigations

- Serial blood glucose monitoring every 1 hr (for 6-8 hrs) till readings > 40 mg%
- Investigations of complications (e.g., Hct, Ca, bilirubin, ABG, CXR, echocardiography...)

## Management

### A) Antepartum Management

- Antenatal care for early diagnosis & control of DM
- Proper assessment of gestational age
- Antepartum assessment of fetal well being (= Diagnosis of placental insufficiency??)
- Assessment of fetal functional maturity (lung maturity, how?)
- Diagnosis of fetal congenital anomalies
- Steroids for prevention of RDS
- Delivery in an equipped hospital

### B) Intrapartum Management

- Intrapartum assessment of fetal well being??
- Resuscitation & Stabilization
- Proper management of expected complications (↓↓ G, Resp. support, birth injury...)

### C) Postpartum Management

- Nursery care (*as before*)
- Management of potential complications
  - Nutrition & hypoglycemia (*see before*)
  - Respiratory complications: Respiratory support
  - Neonatal jaundice, Polycythemia, hypocalcemia, hypomagnesemia (*discuss briefly*)
  - Hypertrophic cardiomyopathy
    - Propranolol
    - Digitalis & other inotropic agents are contraindicated "Obstructive lesion"
    - Resolution usually occurs by the age of 2 wks

## Prognosis

- Childhood obesity
- Impaired intellectual development (neonatal hypoglycemia, polycythemia, birth injury...)

# Beckwith-Wiedmann Sndrome

## Etiology

Sporadic (? familial)

## Clinical Picture

- |                                      |                                      |
|--------------------------------------|--------------------------------------|
| ▪ Fetal overgrowth                   | ▪ Omphalocele                        |
| ▪ Macrosomia                         | ▪ Characteristic ear lobe crease     |
| ▪ Macroglossia                       | ▪ Hemihypertrophy                    |
| ▪ Polycythemia                       | ▪ Hypoglycemia                       |
| ▪ Visceromegaly (HSM & nephromegaly) | ▪ ↑↑ risk of neoplasms (Wilms tumor) |

## Investigations

- Serial blood glucose monitoring
- Genetic studies: Partial duplication of chromosome 11p

## Treatment

Persistent hypoglycemia

## Prognosis

Poor

## Birth Injury

### Definition

- Any mechanical or anoxic trauma occurring in the infant during labor or delivery
- It may be avoidable or unavoidable
- It may be due to deficient medical skill or attention or not

### Incidence

3: 1000 live births with a mortality of 3.7:100.000

### Predisposing Factors

- Cephalopelvic disproportion
- Abnormal presentation (Breech...)
- Prematurity
- VLBW
- Prolonged labor
- Precipitate labor
- Instrumental delivery
- Macrosomia
- Maternal factors: Short stature, primiparity

## Cranial Injuries

### 1. Caput succedaneum, Cephalhematoma, Subgaleal hemorrhage

	Caput succedaneum	Cephalhematoma	Subgaleal hemorrhage
Composition	Edema	Blood	Blood
Site	SC tissue Over the presenting part	Subperiosteal Parietal bone* ( $\pm$ bilateral)	Under aponeurosis Entire length of the scalp
Onset	At birth	Few hours after birth	At birth
Extent	Cross suture lines	Localized by suture lines	Cross suture lines
Consistency	Soft (edema)	Firm ( $\pm$ fracture)	Fluctuant
Resolution	Few days	Weeks to months	2-3 weeks
Associations	Skin ecchymosis	Fracture, anemia, jaundice	Fracture, anemia, jaundice
Investigation	No	Hb%, bilirubin, X-ray, CT	Hb%, bilirubin, X-ray, CT
Rx	No	Anemia, jaundice Aspiration is CI	Anemia, jaundice Aspiration is CI

#### Cephalhematoma Vs Cerebral Meningocele:

2. Pulsating
3. Tense on crying
4. Skull X-ray: Bone defect

2. Skin (Erythema, abrasions, ecchymosis): Forceps delivery

3. Eye (Subconjunctival & retinal hemorrhage): 2ry to  $\uparrow\uparrow$  ICT during delivery of the chest

4. Skull fractures

a. Linear\*: No symptoms, No Rx

b. Depressed: Focal neurological manifestations. Surgical elevation is recommended even if asymptomatic



# Intracranial Hemorrhage

## Incidence

- ↑↑ with ↓↓ gestational age & birth weight
- 10-20% of infants 1.000-1.500 gm
- 60-70% of infants 500-750 gm

### Germinal Matrix:

- Immature capillary network overlying the caudate nucleus
- It disappears at ≈ 32 wks

## Sites

1. Extracerebral: Subdural, Epidural, Subarachnoid
2. Parenchyma
3. Intraventricular: From subependymal germinal matrix or choroid plexus

Full-term → IVH & Subependymal germinal matrix hemorrhage

Premature → Subdural & Subarachnoid hemorrhage (Traumatic)

## Pathogenesis

The major neuropathologic lesions in VLBW are:

- A) IVH: From subependymal germinal matrix or choroid plexus
- B) Periventricular leukomalacia (PVL):
  - Pathology: White matter damage in the periventricular area
  - Cause: Hypoxia, ischemia, IVH, systemic BP fluctuation with impaired cerebral autoregulation (= Maintenance of cerebral BF over a wide range of BP)
  - Result: Motor abnormalities, CP
  - Prevention: Antenatal steroids, PGs inhibitors (Indomethacin)
  - Diagnosis: Cystic lesions of PVL become evident on cranial US ≥ 3 wks after the insult

## Etiology

### A) Vascular & Extravascular structural factors

- ☒ Trauma: See before ( )
- ☒ Hypoxic-ischemic injury to the germinal matrix
- ☒ Congenital vascular anomalies
- ☒ Bleeding tendency: Thrombocytopenia, Coagulopathy, DIC (*Discuss*)

### B) ↑↑ Inflow (↑↑ Cerebral BF)

- ☒ Convulsions
- ☒ Hypertension
- ☒ Hypercapnia & Hypoxemia
- ☒ Apnea
- ☒ PDA
- ☒ Infusion of hyperosmolar solution (NaHCO<sub>3</sub>)
- ☒ Excessive manipulation of the NB

### C) ↓↓ Blood Outflow

- ☒ HF
- ☒ Pneumothorax
- ☒ RD
- ☒ CPAP & ↑↑ PEEP
- ☒ Labor process

## Clinical Picture

Onset: 50% of cases occur on D1, 75% within the 1<sup>st</sup> 3 days

1. Blood loss: Pallor, Jaundice, RD, Shock

2. ↑↑ ICT

- Bulging AF
- ↑↑ Head circumference
- High-pitched cry
- Poor activity
- Poor suckling
- Lethargy/Irritability
- Weakness
- Hypotonia
- Muscle twitches
- Seizures

3. Brain stem manifestations

- Apnea
- Temperature instability
- Cranial nerve palsy
- Lost light reflex
- Nystagmus
- Abnormal gaze

4. Intracerebral hemorrhage

- Coma
- Focal neurological deficits: Focal seizures, hemiplegia...

## Investigations

A) Laboratory

- CBC:
  - Unexplained anemia
  - Thrombocytopenia
- ↑↑ unconjugated bilirubin (Without evidence of hemolysis)
- ABG: Hypoxia, Hypercapnia, Acidosis

Unexplained ↓↓ Hct in a neonate:

- ICH
- Subcapsular hematoma of the liver

B) Imaging

- Cranial US
  - Bed-side method
  - Indications:
    - Routine: for all preterm neonates < 1.500 gm or GA < 34 ks
    - F/U: To detect & monitor complications (e.g., hydrocephalus...)
    - Clinical indications
  - Timing: Within the 1<sup>st</sup> 7-14 days & at 36 wks PCA
  - Interpretation:



### Grades of Subependymal & IVH:

- Grade I: Isolated subependymal Hge
- Grade II: IVH + No dilatation
- Grade III: IVH + Ventricular dilatation
- Grade IV: Parenchymal Hge

### Grades of Ventricular dilatation:

- Normal: < 0.5 cm
- Mild: 0.5-1 cm
- Moderate: 1-1.5 cm
- Severe: > 1.5 cm

• CT & MRI

- Require infant transport which may be risky
- More sensitive in detection of subdural & intraparenchymal hemorrhage

C) Invasive

• Lumbar puncture (CSF)

- Indications:
  - ↑↑ ICT
  - Diagnosis of subarachnoid hemorrhage
  - Diagnosis of CNS infection
- Complications: Apnea, bradycardia, circulatory insufficiency

## Prevention

- Proper antenatal care & careful management of obstetric problems (C/P disproportion)
- Prevention of prematurity
- Antenatal steroid therapy [Beta- or Dexa-, Betamethasone also ↓↓ PVL]
- Postnatal PG inhibitors (Low-dose Indomethacin): ↓↓ incidence of severe IVH
- Avoid hyperosmolar solution
- Avoid excessive manipulation
- Rx of maternal immune diseases associated with neonatal thrombocytopenia (ITP, SLE)??
- Rx of NATP??
- Vitamin K
  - Antenatal: to the mother receiving phenytoin or phenobarbitone
  - Postnatal: neonatal resuscitation

## Monitoring

- a. Clinical: Vital signs, Pallor, jaundice, RD
- b. Laboratory: Hct%, ABG, electrolytes, blood glucose
- c. Imaging: F/U Cranial US (Why??)

## Treatment

- Incubator: Isolation, observation
- Vitamin K, FFP, fresh packed RBCs
- Seizures: Anticonvulsants
- Jaundice, DIC,
- Management of complications: Post-hemorrhagic hydrocephalus
  - Incidence: 10-15%
  - Diagnosis: Cranial US, CT brain
  - Types: Communication or obstructive
  - Treatment
    - F/U: Arrested hydrocephalus
    - Repeated LP: risk of infection
    - Repeated ventricular taps: Risk of infection & puncture porencephaly
    - V/P shunt: Persistent hydrocephalus
    - Ventriculosubgallial shunt: Closed system for CSF drainage
    - Medical (Acetazolamide): Ineffective

## Prognosis

- Post-hemorrhagic hydrocephalus
- Parenchymal damage: Cerebral palsy (Spastic), learning difficulties
- Grades I, II: Normal outcome (similar to normal US)
- Poor prognosis in grades III, IV

## Brain Injury from Inflammation, Infection & Medications

A) IVH (Severe) & PVL

B) Inflammation: NEC

C) Infections:

- a. In-utero: Congenital infections
- b. Postnatal: Bacterial meningitis
- c. Maternal chorioamnionitis

D) Medications: Postnatal steroids

- a. Within the 1<sup>st</sup> wk of life: Poor growth, sepsis, bowel perforation
- b. After the 1<sup>st</sup> wk of life: CP & developmental delay

### Mechanism:

- Cytokine release
- SIRS

## Spine & Spinal Cord Injury

### Etiology

Traction on the spine during difficult labor:

- Cephalic: Delivery of shoulder
- Breech: Delivery of the after-coming head

### Pathology

- Site: C7 & T1 Vertebrae
- Pathology: Edema, hemorrhage, fracture or transection

### Clinical Picture

- Onset: At birth (Transection) or delayed within the 1<sup>st</sup> wk (Edema or Hge)
- Quadriplegia: Flaccid (Early) then spastic (Later on)...
- Vital signs: Respiratory depression, Hypotension, Hypothermia

### Treatment

- Removal of compression
- Supportive: Care of the comatose

## Peripheral Nerve Injury

### A) Brachial Plexus Injury

#### Etiology

Traction on the neck during difficult labor:

- Cephalic: Delivery of shoulder
- Breech: Delivery of the after-coming head

#### Types

	Erb's Paralysis	Klumpke's Paralysis
Root injury	C5, C6	C8, T1
Muscle affected	Deltoid, Biceps, Brachioradialis, Supra- & Infraspinatus-	Intrinsic muscles of the hand
Nature	LMNL	LMNL
Limb Position	Arm: Adduction & Internal rotation Forearm: Pronation Policeman tip	
Reflexes	Absent Moro reflex Intact grasp reflex	Absent grasp reflex
Diaphragmatic	If C4 is injured	
Horner's		If T1 sympathetic fibers are injured
Associations	Diaphragmatic paralysis (C4)	Horner's (T1 sympathetic fibers)
Investigation		
Treatment		
Position (1-2 wks)	90° Adduction, External rotation & Supination	Wrist is splinted (Neutral position) Padding in the fist
Physiotherapy	Gentle range motion exercises (after 2 wks)	
Surgical	Neuroplasty & tendon transfer Not advisable before 3-4 yrs	

## B) Phrenic Nerve Injury

### Etiology

- Usually associated with ipsilateral Erb's palsy
- Usually unilateral

Normally, Respiration is entirely diaphragmatic

### Clinical Picture

- Irregular respiration & cyanosis
- Respiratory movements: Thoracic (No abdominal movements)

### Investigations

- Fluoroscopy:
  - Elevation of the diaphragm
  - Seesaw movements (Paradoxical movement)

### Treatment

- Position: On the affected side (Why?)
- Respiratory support... + antibiotics
- Nutrition: IVF then Ryle or oral
- Surgical plication of the diaphragm is rarely indicated (Spontaneous recovery in 1-3 ms)

## C) Facial Nerve Injury

### Etiology

- Usually unilateral (If bilateral, suspect congenital cause)

### Types



	Peripheral	Central
Frequency	More common	Less common
Cause	Pressure on the facial nerve (Hge, edema, forceps)	Facial nuclear agenesis ICH
Nature	LMNL (as Bell's palsy)	UMNL
Part of the face	One side of the face (upper & lower)	Only the lower part
Eye exposure	Yes	No
Treatment		
Eye prophylaxis	Indicated (Methylcellulose)	Not indicated
Surgical	Neuroplasty if nerve fibers are torn	

## D) Other Peripheral Nerves

### Injury of Sternomastoid Muscle

#### Etiology

#### Pathology

- Hematoma: Within hours after birth
- Organization & Fibrosis: Muscle shortening + Mass (Sternomastoid tumor)

Clinical Picture Mass, Torticollis, Eye problems

Treatment Physiotherapy

## Injury of Visceral organs

	Liver (& Spleen)	Adrenal gland
<b>Cause</b>	<ul style="list-style-type: none"> <li>▪ Pressure on the liver (Breech)</li> <li>▪ Incorrect cardiac massage</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pressure (Breech)</li> <li>▪ HIE, Sepsis</li> </ul>
<b>Pathology</b>	Subcapsular hematoma	Adrenal hge (90% unilateral, Rt>Lt)
<b>Clinical Picture</b>	<ul style="list-style-type: none"> <li>▪ Normal: 1-3 days</li> <li>▪ Blood loss: Pallor, ↑↑ HR, ↑↑ RR</li> <li>▪ Jaundice</li> <li>▪ Mass (Rt hypochondrium)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Normal: 1-3 days</li> <li>▪ Blood loss: Pallor, ↑↑ HR, ↑↑ RR</li> <li>▪ Jaundice</li> <li>▪ Mass (Flank)</li> <li>▪ Asymptomatic: Calcified hematoma</li> </ul>
<b>Diagnosis</b>	<ul style="list-style-type: none"> <li>▪ Early clinical suspicion</li> <li>▪ Abdominal US</li> </ul>	<ul style="list-style-type: none"> <li>▪ Early clinical suspicion</li> <li>▪ Abdominal US, CT &amp; MRI</li> <li>▪ Na, K, Glucose, ABG</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>▪ Packed RBCs</li> <li>▪ Jaundice</li> <li>▪ Surgical repair</li> </ul>	<ul style="list-style-type: none"> <li>▪ Packed RBCs</li> <li>▪ Jaundice</li> <li>▪ Rx of adrenal insufficiency</li> </ul>

## Fractures

### Fracture Clavicle

**Incidence** Commonest fracture

**Etiology**

- Shoulder dystocia
- Breech delivery

**Clinical Picture**

- No active movement of the affected limb
- Absent Moro reflex
- Crepitus
- Mass (Callus formation)

**Treatment**

- Immobilization of the affected limb
- Excellent prognosis

### Fracture Long Bones

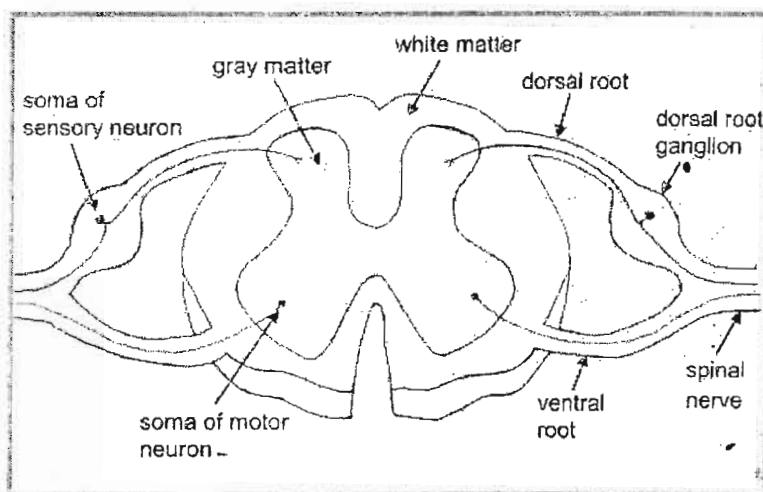
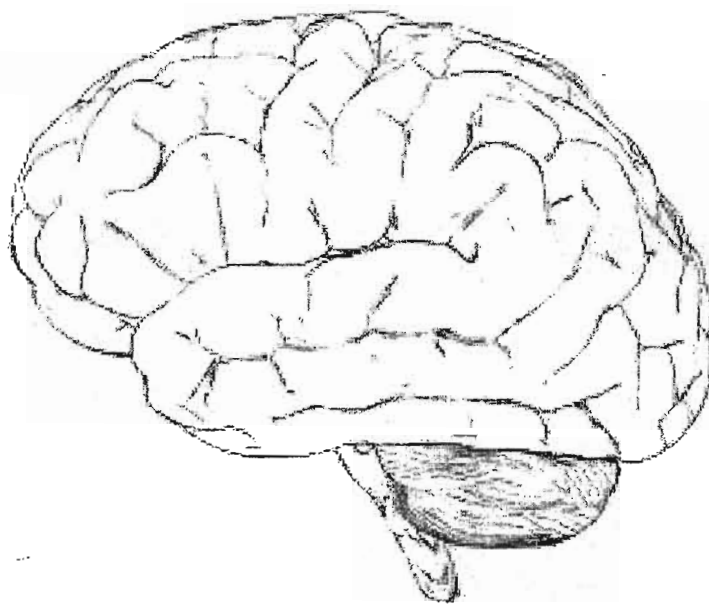
- No active movement of the affected limb
- Absent Moro reflex (UL)
- Immobilization of the affected limb

### Fracture Nose

- Fattening of the nose with asymmetric nares

### Dislocation & Epiphyseal separation

- No active movement of the affected limb
- Swelling
- Diagnosis: X-rays
- Immobilization of the affected limb ± Surgery



# **Pediatric Neurology**

By

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# Neuromuscular Disorders

## (Motor unit disorders)

### Definition

- Diseases of the AHC, peripheral nerves, N/M junctions or the muscles (= LMNL)
- They have certain **features** that differentiate them from UMNL

	Below the level of the lesion	At the level of the lesion
<b>Paralysis</b>	Below the level of the lesion	At the level of the lesion
<b>State of muscles</b>	No wasting (except late)	Early & marked wasting
<b>Fasciculations</b>	Absent	May be present (AHC irritation)
<b>Tone</b>	Hypertonia	Hypotonia
<b>Deep reflexes</b>	Hyperreflexia	Hyporeflexia
<b>Pathological Reflexes</b>	May be present	Absent
<b>Clonus</b>	May be present	Absent
<b>Superficial Reflexes</b>	Lost	Lost (if the reflex arc is affected)
<b>Plantar Reflex</b>	Positive (Dorsiflexion of big toe ± Fanning of other toes)	Plantar flexion ( <i>Normal response</i> ) Or No response

### General Features (LMNL)

1. **State of the muscle:** Usually thin
2. **Tone:** Hypotonia
3. **Power:** Weakness/paralysis
  - Myopathy: Proximal (except in myotonic dystrophy)
  - Neuropathy: Distal (except in juvenile SMA)
4. **Muscle pain (Myalgia):** in neuropathy & inflammatory myopathy
5. **Muscle contractures:** Congenital arthrogryposis or acquired (due to nerve or muscle disease)
6. **Fasciculations:** AHC disease (SMA)
7. **Sensory manifestations:** Indicates neuropathy
8. **↓ Fetal movements & polyhydramnios**
9. **Chest infection & Nutritional defects**
10. **Delayed motor milestones, undescended testicles**

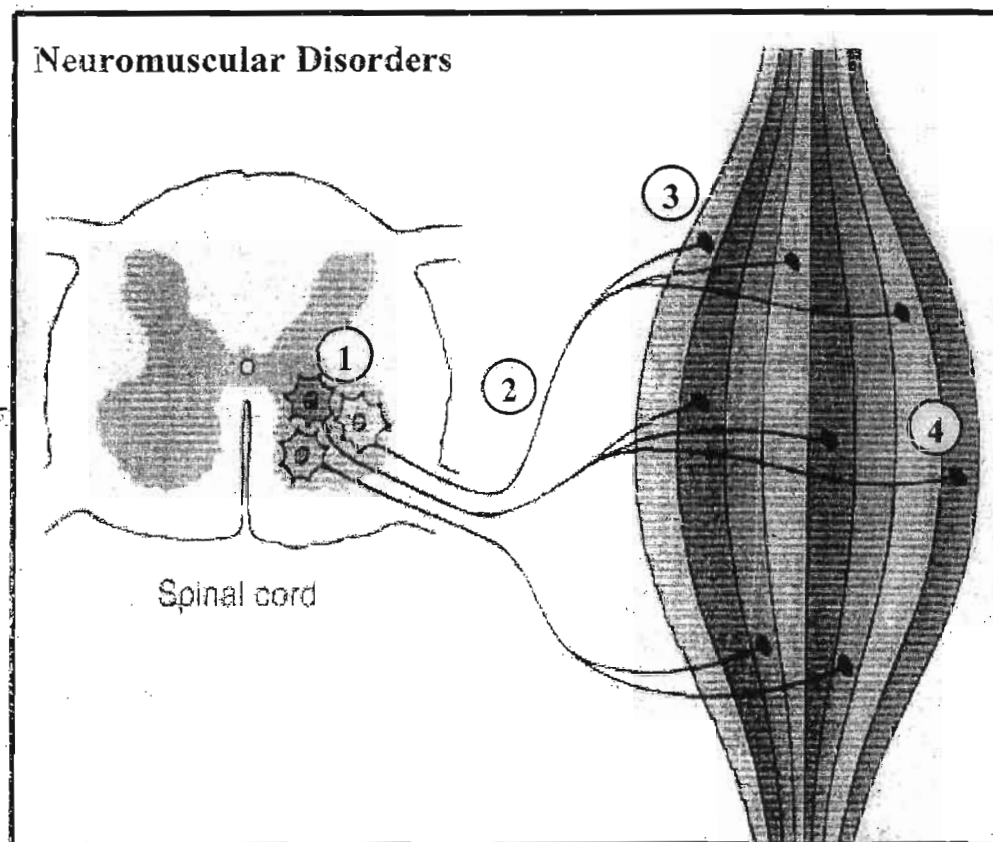
### General Investigations

- Serum creatine kinase (CK):
  - Present only in 3 organs: Skeletal muscle (MM), Cardiac muscle (MB), Brain (BB)
  - Characteristically ↑↑ in DMD
- Nerve conduction velocity (NCV): 80% of the total nerve fibers must be involved
- Electromyography (EMG): Myotonia, decremental response (**NB:** CK may ↑↑ after EMG)
- Muscle biopsy:
  - Procedure: Quadriceps femoris under LA
  - Test: Biochemical (enzymes), histochemical & immunohistochemical (dytrophin, merosin)
  - DD of myopathic vs neurogenic processes
  - Diagnosis of the type of myopathy & specific enzymatic deficiencies
- Nerve biopsy: Sural nerve (**NB:** Regeneration of the nerve occurs in > 90%)
- Imaging of the muscle: US, CT, MRI
- Cardiac assessment: Electrocardiography (ECG), Echo-
- Genetic analysis: Blood samples or in muscle biopsy



## **Treatment** (Supportive)

- Respiratory support
- Nutritional support
- Rx of chest infection
- Physiotherapy
- Orthopedic care



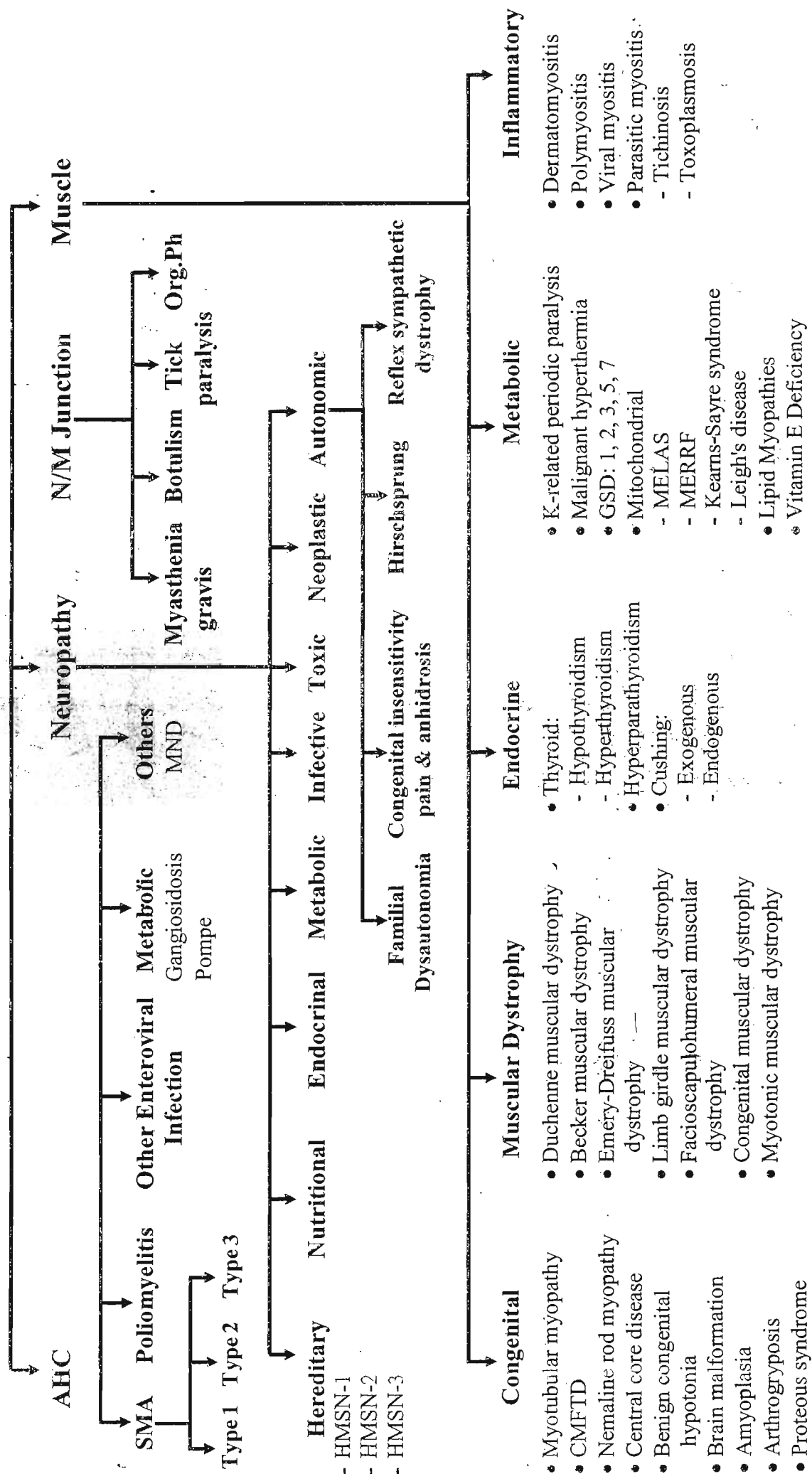
## **Presentations of N/M disorders**

1. Floppy infant: Infant with severe persistent hypotonia
2. Acute paralysis: Rapid loss of previously acquired motor skills (hours-days)
3. Progressive motor weakness: Gradual loss of previously acquired motor skills (wks-yrs)
4. Delayed motor development

### **Remember**

- All N/M diseases show LMNL characters, but they differ in their clinical presentations
- Each N/M disease has its own clinical specific features

# **Neuromuscular Disorders**



# Anterior Horn Cell Disease

## Spinal Muscular Atrophy

### Definition

- It is degenerative disease of AHC in the spinal cord & brain stem (motor cranial nuclei)
- Starting in the IU life & continue in infancy

### Etiology

- Autosomal recessive (SMN gene on chromosome 5)
- It is the 2<sup>nd</sup> most common N/M disease (following DMD)
- Failure to arrest apoptosis (Apoptosis = Programmed cell death)
- Pathology: Degeneration

### Classification

Type	Synonyms	Severity	Functional ability
SMA type1	Werdnig-Hoffmann	Severe	Unable to sit
SMA type2*	Late infantile	Intermediate	Able to sit
SMA type3	Juvenile = Kugelberg-Welander	Mild	Able to walk
SMA type0	Fetal	Severe	Perinatal death

### Clinical Picture

**Tongue Fasciculations**

- Antenatal history: ↓↓ Fetal movements & polyhydramnios
- Floppy infant, How? 3 tests (Head lag, ventral suspension & frog leg)
- LMNL: Wasting, weakness, hypotonia, hyporeflexia
- Paradoxical chest wall movements
- Bulbar symptoms: Dysphagia, dysarthria, hoarseness of voice & nasal regurgitation
- Recurrent chest infection & aspiration
- Normal mentality, sensation, extra-ocular muscles & sphincters
- **Fasciculations:** Best seen in the tongue
- **Prognosis (Type 1):** Death in infancy (Respiratory failure & respiratory infections)
- SMA type 2: Late infancy & slowly progressive
- SMA type 3: Delayed onset (early childhood), weakness is (**Proximal** > Distal)

**Purely Motor**

### Investigations

- Electromyography (EMG): Denervation pattern (Fibrillation potentials)
- Serum CK & NCV: Normal
- Molecular genetic diagnosis
- Prenatal genetic diagnosis is available

### Treatment

- Supportive
- Antioxidants
- Valproic acid & Gabapentin



# Poliomyelitis

Purely Motor

## Etiology

Poliovirus (3 types)

Mode of transmission Feco-oral (Developing countries) & Droplet (Developed countries)

## Sequelae

- ☒ Asymptomatic (Unapparent): 90-95%
- ☒ Manifest
  - Abortive: Mild respiratory &/or GIT symptoms
  - CNS involvement:
    - Non-paralytic: Meningeal irritation
    - Paralytic: Spinal, bulbar or both (AHC affection)

## Clinical Picture (Purely Motor)

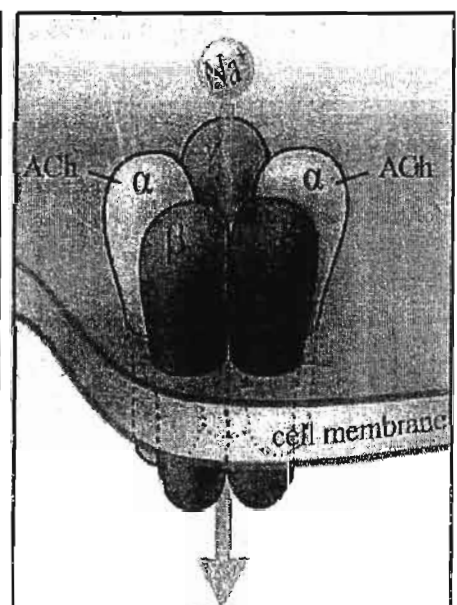
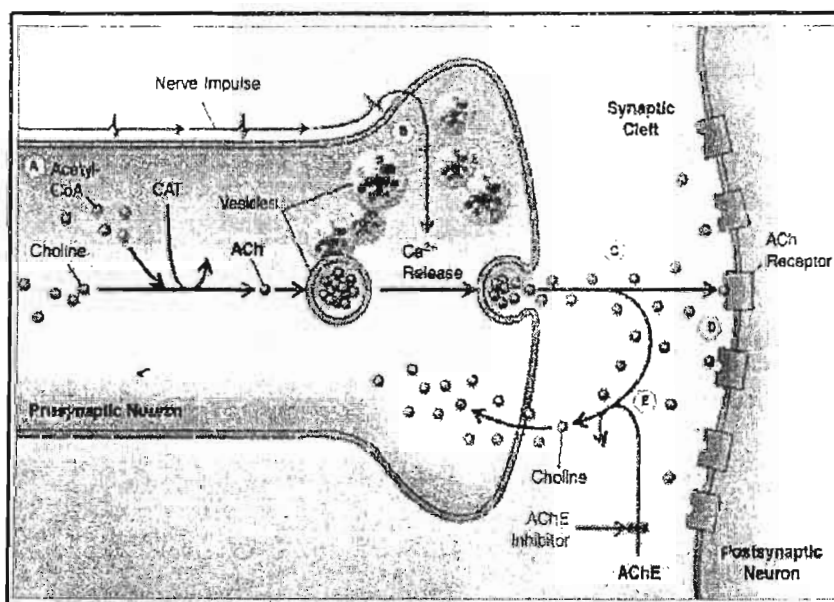
- Acute onset of Asymmetric flaccid paralysis usually affecting the lower limbs
- Bulbar symptoms (Dysphagia, dysarthria, hoarseness of voice & nasal regurgitation)

Diagnosis Clinical + Virus isolation + Serology

Prevention Sanitation, Vaccines (OPV & IPV)

Treatment Rest, physiotherapy & orthopedic care

## Neuromuscular Junction Disorders



Nerve impulse reaches the nerve terminal  
 Acetylcholine is released  
 Binding of receptors on motor endplate  
 Opening of ion channel: Depolarisation (Muscle AP)  
 Muscle contraction  
 AChE degrades ACh

ACh Receptor  
 Formed of 5 subunits  
 2  $\alpha$ , 2  $\beta$ , 1  $\gamma$

# Myasthenia Gravis

## Definition

It is disorder of N/M junction transmission due to:

- Anti-ACh receptors antibodies: in **immune**-mediated MG & **transient** myasthenia
- Congenital defect in the N/M junction

## Etiology

### 1. Autoimmune (Juvenile & adult MG)

- Anti-ACh receptors antibodies
- May be associated with collagen-vascular diseases or thyroid diseases (Hashimoto)
- In adults, it may be associated with thymoma or lung cancer (**Eaton-Lambert syndrome**)

### 2. Congenital (CMS): mostly AR diseases (No AChRab)

### 3. Transient neonatal myasthenia: Transplacental passage of Ab (Myasthenic mother)

## Clinical Picture

### ☒ Congenital & Transient forms

- Floppy infant
- Weak suckling
- Respiratory support & NGT feeding may be needed
- Transient form is transient!! (Weeks, why?)

**Only the skeletal muscles are affected**

### ☒ Autoimmune form

- Easy fatigability on repetition of movements
- **Descending march**
  - Ocular muscles: ptosis (usually asymmetric), diplopia
  - Facial weakness (*Myasthenic snarl*)
  - Jaw muscles
  - Bulbar symptoms: 4
  - Skeletal muscles (**Proximal** > Distal)
- **Diurnal** variation (worst at the end of the day)

## Clinical Tests

- Upward gaze
- Jaw chewing
- Opening & closing of the fist
- UL elevation

## Investigations

- Serum CK & NCV: Normal
- EMG: **Diagnostic (Decremental response** with repetitive nerve stimulation)
- Anti-ACh-receptors antibodies: Positive in 30% of affected adolescents
- Muscle-specific tyrosine kinase Ab (MuSK): Positive in 70% of AChRab-negative patients
- Association: ANA, Thyroid functions
- CXR & Chest CT: Thymus
- Congenital myasthenia: Microelectrode studies of motor endplate potentials (EPP)
- **Tensilon test** [Short-acting anti-cholinesterase]: should be done in **emergency** department
  - ☒ **IV Edrophonium (0.1 mg/Kg)**: Improvement within 10 sec
  - ☒ **IM Prostigmine (0.04 mg/Kg)**: Improvement within 30 minutes

**Atropine is given before the test??**

## Treatment

☒ Autoimmune form

- Prostigmine (*Neostigmine*): 0.4 mg/Kg/6 hr PO
- Pyridostigmine (*Mestinon*) (longer-acting)
- Steroids
- Thymectomy
- Plasmapheresis (**Myasthenic crisis**)
- IVIG (**Myasthenic crisis**)

☒ **Transient forms:** Anti-Cholinesterase for few weeks

**ⓧ Congenital forms:** Options include ephedrine, anti-cholinestrases ...

## Prognosis

### Remission, Crises, Complications of treatment

### Crises in Myasthenia:

- A) **Myasthenic crisis:** May be precipitated by infection, surgery or drugs  
Manifestations: Respiratory weakness, bulbar symptoms  
TTT: Support + IVIG or plasmapheresis (severe cases)
- B) **Cholinergic crisis:** Due to overtreatment  
Manifestations: DUNBBELS  
TTT: Withdrawal

## Avoid

- ▶ Amygdalin/lotosides
- ▶ Ciprofloxacin
- ▶ Chloroquine
- ▶ Flucanazole
- ▶ Fluoxetine
- ▶ Furosemide
- ▶ Naloxone
- ▶ Nifedipine
- ▶ Nystatin
- ▶ Sildenafil
- ▶ Tamoxifen

## Tick Paralysis

### Causative Organism

- Wood or dog tick (embeds its head into the skin) → Neurotoxin → Block ACh release
- Tick → Neurotoxin → Block ACh release

## Clinical Picture

- Motor: Weakness
- Sensory: Tingling

**Treatment** Complete removal of ticks

# **Botulism**

## **Causative Organism**

- Clostridium botulinum (Gram positive, spore-forming, anerobic bacteria)
- Clostridium botulinum → Neurotoxin → Block ACh release
- Spores are heat-resistant, but toxin is heat-labile

## **Epidemiology**

### **1. Infant botulism**

- Infectious disease (ingesting the spores) e.g., honey
- Honey is **unsafe** food for any child < 1 yr
- Age: 2-6 months
- Not in Africa

**2. Food-born botulism:** Ingestion of ready-made toxin (canned foods, dried fish...)

**3. Wound botulism:** Crush injuries

**4. Inhalation botulism:** Biologic terrorism

**5. Iatrogenic botulism:** Overdose of therapeutic or cosmetic use of botulinum toxin

## **Clinical Picture** (Purely Motor)

- Incubation period is short (Few hours)
- Cranial nerve involvement (Ptosis, diplopia, bulbar...)
- Symmetrical descending flaccid paralysis
- Constipation is an early important symptom in infantile botulism
- Food-born botulism: 30% have nausea, vomiting, diarrhea

**Purely Motor**

**No Fever**

**Do Not diagnose botulism without bulbar symptoms**

## **Investigations**

- Serum: botulinum toxin
- Stools & food remnants: botulinum toxin & organism
- EMG: Variable (Potentiation of muscle potentials with high frequency stimulation)

## **Differential Diagnosis**

**A. Acute flaccid paralysis**

**B. Infant Botulism:** Sepsis, CNS infection, dehydration, pneumonia, SMA, poliomyelitis, GBS, myasthenia, organophosphorus poisoning, tick paralysis, intoxication, metabolic (MCAD deficiency)

## **Treatment**

- Infant botulism: Human botulism immunoglobulin (BIG-IV)
- Other types: Equine heptavalent botulinum antitoxin (H-BAT)
- Respiratory support (Positioning, ETT, mechanical ventilation)
- Nutritional support (NGT)
- Avoid aminoglycosides

## **Prognosis**

Full complete recovery is expected in properly treated patients (4-6 weeks)

## **Complications**

- Nosocomial: infections, pneumonia, ARDS
- Iatrogenic: Mechanical ventilation -related complications, hyponatremia
- SIADH

# Organophosphorus Poisoning

## Etiology (Source)

1. Insecticides
2. Contaminated food

Action: Anti-Cholinesterase

## Pathophysiology

DUMBBELS

- Binding & inhibition of acetylcholinesterase
- Accumulation of acetylcholine
- If untreated: It will be irreversible (Aging of the enzyme). Regeneration need wks-months

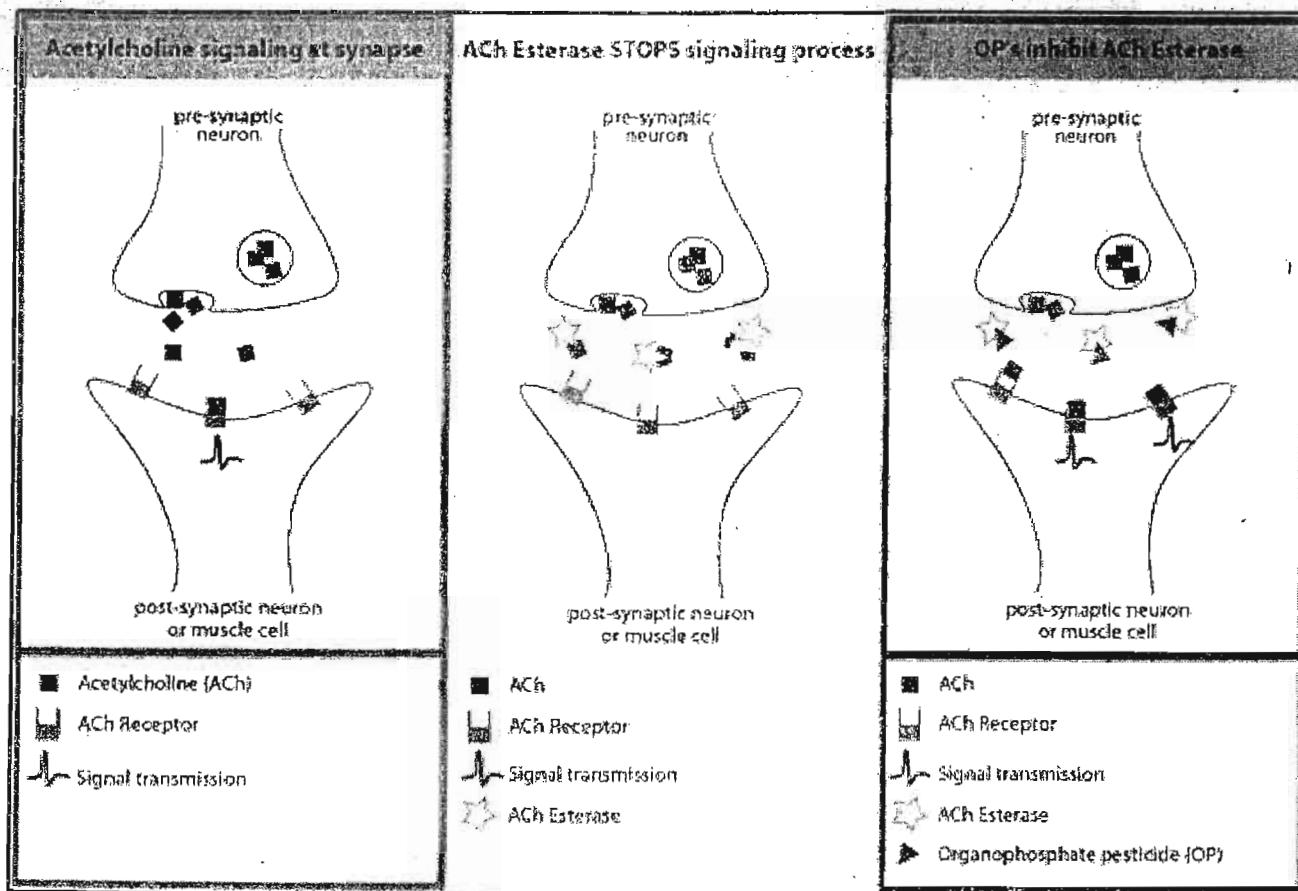
## Clinical Picture

- Diarrhea, urination, miosis, bronchorrhea, bronchospasm, bradycardia, emesis, lacrimation, salivation, sweating
- Nicotinic manifestations: Weakness, paralysis, tachycardia, HTN
- Severe cases: Confusion, coma, seizures, arrhythmias, respiratory failure

## Treatment

- Supportive care...
- Activated charcoal
- Atropine (0.1 mg/Kg q 5-10 min): (usually large doses are needed)
- Pralidoxime (25 mg/Kg): Reactivates the recently inhibited enzyme "before aging"

Enzyme reactivator





# Peripheral Neuropathy

## Definition

It is inflammation of the peripheral nerves &/or the cranial nerves

## Classification

### A) Etiologically:

#### 1. Hereditary

- Hereditary motor sensory neuropathy (Types 1, 2, 3), GAN, CHN
- Roussy-Levy Syndrome (HMSN type 1 + Friedrich's ataxia)

#### 2. Nutritional: Vitamin B<sub>1</sub>, B<sub>6</sub>, B<sub>12</sub> deficiency & Pellagra (Niacin deficiency): 3"D"

#### 3. Endocrinal: DM, Hypothyroidism & Hyperthyroidism

#### 4. Metabolic

- CRF (uremia): ↑↑ PTH
- Fabry, Refsum disease, porphyria, tyrosinemia, DM
- Leukodystrophy (Krabbe's, metachromatic leukodystrophy, adrenoleukodystrophy)

#### 5. Infective: Diphtheria, Guillain-Barre syndrome

#### 6. Toxic

- Drugs: Phenytoin, penicillamine, metronidazole, INH, vincristine, cisplatin, ethanol
- Heavy metals: Lead (purely **motor**), Arsenic (mainly **sensory**), Mercury, Gold
- Occupational: Organophosphorus, hexacarbons, cyanide, ethylene oxide

#### 7. Neoplastic: Lymphoma (*Paraneoplastic*)

#### 8. Autonomic

### B) Pathologically:

#### 1. Axonopathy: Axonal degeneration

#### 2. Myelinopathy: Demyelination

### C) Clinically:

#### 1. Number: Mononeuropathy & polyneuropathy

#### 2. Type: Motor, sensory or autonomic

##### a. Motor

Nature: LMNL

Distribution:

Bilateral & symmetrical

LL > UL

Distal > Proximal

Extensors > Flexors

Foot drop

High steppage gait

Lost ankle & preserved knee reflex

Cranial nerves may be affected

Stabilization of the ankle

##### b. Sensory

Irritation

Pain & Parasthesia

Muscle pain

Destruction

Superficial sensory loss (Glove & stocking nature)

Deep sensory loss (Sensory ataxia)

Carbamazepine for Pain

##### c. Autonomic

Vasomotor: Coldness & Cyanosis

Cutaneous: Hair loss, brittle nails, trophic ulcers

Avoid traumatic injury

# Hereditary Motor Sensory Neuropathy

## Peroneal Muscular Atrophy (HMSN Type 1)

Charcot-Marie-Tooth

### Etiology

- AD<sup>17</sup>
- It is the most common genetically determined neuropathy

### Clinical Picture (Onset = Late childhood)

- Weakness & wasting affecting the leg muscles & the lower 1/3 of the thigh → **Inverted bottle appearance**
- There is marked **discrepancy** between the degree of wasting & weakness
- Skeletal anomalies: pes cavus & kyphoscoliosis
- Sensory & autonomic manifestations

### Investigations

- NCV: ↓↓ Nerve conduction
- Sural nerve biopsy: Axonopathy & myelinopathy (Onion bulb appearance)
- Genetic analysis

## Peroneal Muscular Atrophy (HMSN Type 2)

### Manifestations as HMSN-1 but...

- AD<sup>1</sup>
- Onset: 2<sup>nd</sup> decade
- Milder
- More slowly progressive
- Sural nerve biopsy: Axonopathy (axonal degeneration)

## Dejerine-Sottas Disease (HMSN Type 3)

### Manifestations as HMSN-1 but...

- AD<sup>17</sup>
- Early onset (Infancy)
- More severe
- More rapidly progressive
- Sural nerve biopsy: ↑↑ formation of onion bulb (Intertitial hypertrophic neuropathy)

## Roussy-Levy Syndrome (HMSN Type 1 + Friedreich's ataxia)

Type	Genetics	Onset
HMSN type1	AD or AR	1 <sup>st</sup> decade
HMSN type2	AD or AR	2 <sup>nd</sup> -3 <sup>rd</sup> decade
HMSN type3	AD	1 <sup>st</sup> year

## Other Hereditary neuropathies

### Giant Axonal Neuropathy

Pathology Focal axonal enlargement

C/P Floppy infant (Hypotonia), ataxia & reddish hair

### Congenital Hypomyelinating Neuropathy

Pathology Lack of normal myelination of peripheral nerves (DD: leukodystrophy)

C/P Floppy infant (Hypotonia) & developmental delay

### Refsum Neuropathy

Etiology AR<sup>10</sup>

Pathogenesis Failure of  $\alpha$ -FA oxidation  $\rightarrow$  accumulation of phytanic acid

C/P Polyneuropathy, ataxia, retinitis pigmentosa, blindness, deafness, ichthyosis (scaly skin)

Investigations  $\uparrow\uparrow$  Serum phytanic acid,  $\downarrow\downarrow$  NCV

Treatment  $\downarrow\downarrow$  Dietary phytanic acid (nuts, coffee)  
Plasmapheresis

### Fabry Neuropathy

Etiology XLR

Pathogenesis

-  $\downarrow\downarrow$   $\alpha$ -galactosidase (*ceramide trihexosidase*)  $\rightarrow$  accumulation of ceramide trihexoside

C/P

- Recurrent episodes of burning pain and paresthesias
- Anhidrosis
- Angiokeratoma corporis diffusum: Thighs, buttocks, lower abdomen & groin
- Ocular: Corneal opacity & cataract
- Recurrent strokes
- Hypertension and renal failure

Investigations

- $\alpha$ -galactosidase activity
- Skin or sural nerve biopsy specimens:
- *Zebra bodies* in endothelial cells, arterioles & Schwann cells, best demonstrated by EM
- Renal evaluation

Treatment

- Enzyme replacement therapy
- Pain management

### Ataxia Telangiectasia

### Leukodystrophies

Krabbe disease, metachromatic leukodystrophy & adrenoleukodystrophy

### Hypermyelinating (Tomaculous) Neuropathy

# Mononeuropathies

## Bell Palsy



### Definition

It is acute isolated unilateral facial nerve palsy

### Etiology

- Postinfectious immune inflammation (Myelopathy)
- Preceding infection: Viral (HSV\*, VZV\*, EBV, CMV, mumps) or mycoplasma

### Clinical Picture

- Facial palsy of LMNL nature (Complete paralysis of the ipsilateral 1/2 of the face)
  - Absence of forehead wrinkles
  - Absent nasolabial fold
  - Inability to raise the eyebrows
  - Inability to close the eye (exposure keratitis)
  - Deviation of the angle of the mouth to the healthy side
  - Drooping of the angle of the mouth (with dribbling of saliva)
  - Inability to blow the cheeks
  - Inability to show the teeth
- Loss of taste sensation of the anterior 2/3 of the tongue on the same side of the lesion

### Differential Diagnosis

- ☒ **Congenital Facial nerve palsy:** Absent facial nucleus
- ☒ **Neoplastic:** Cerebellopontine angle tumors (acoustic neuroma), Neurofibroma, Leukemia
- ☒ **Traumatic:** Birth injury (forceps)
- ☒ **Vascular:** Infarction
- ☒ **Apparent facial palsy:** Absent depressor angularis muscle (Not facial palsy)

### Treatment

- **Prednisone** (1 mg/Kg/day) for 1 week followed by tapering over 1 week
- Eye protection (Methylcellulose eye drops)
- Acyclovir??
- Physiotherapy in chronic cases

### Prognosis

- Complete recovery in > 85%
- Residual mild facial weakness in 10%
- Residual severe facial weakness in 5%

## Congenital Ptosis

### Etiology

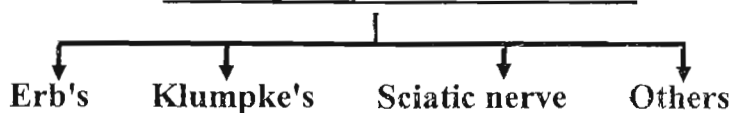
1. Faulty innervation of levator palpebrae superioris
2. Marcus-Gunn jaw winking syndrome: Aberrant innervation of levator muscle from V nerve

## 6th Nerve Palsy



Convergent squint

## Peripheral Nerves



# **Guillain-Barre Syndrome**

(Postinfectious Polyneuropathy)

## **Etiology**

- Postinfectious polyneuropathy usually following non-specific viral infection
- Preceding infection: **Viral**, Campylobacter jejuni, H.pylori or **Mycoplasma**

## **Pathology**

Myelopathy\* (Demyelination) or axonopathy

**Mainly Motor**

## **Clinical Picture** (mainly Motor)

- History of preceding infection
- Gradual onset & progressive course (over days)
- Weakness or paralysis (LMNL) affecting the lower limbs & ascending to involve the trunk, UL, respiratory & bulbar muscles [**Symmetrical ascending paralysis**]
- Asymmetric in 9%
- Sensory manifestations: Parasthesia and muscle pain & tenderness
- Autonomic manifestations: variability of HR, BP, Temperature
- **Miller-Fisher syndrome**: acute external ophthalmoplegia, ataxia & areflexia
- **Congenital GBS**: Rare [Hypotonia, floppy infant, weakness & areflexia]
- **Chronic variant**: Chronic inflammatory demyelinating polyradiculopathy (CIDP) also called "relapsing or unremitting"

## **Investigations**

- CSF: Cytoalbuminous dissociation
- NCV: ↓↓ Nerve conduction
- EMG: Denervation pattern
- Serology: Campylobacter jejuni & Mycoplasma
- Serum **Antganglioside antibodies** (against G<sub>M1</sub> & G<sub>D1</sub>): specially with axonal type

## **Treatment**

### **1. Acute form**

- ☒ **Hospital admission & supportive measures** (Respiratory, nutritional...)
- ☒ **IVIG**: 400 mg/Kg/day for 5 consecutive days
- ☒ **Plasmapheresis**
- ☒ Steroids are **Not** effective in the acute GBS

### **2. Chronic relapsing or unremitting GBS**

- ☒ **Steroids** (Oral or Methylprednisolone pulse therapy)
- ☒ **IVIG**: 400 mg/Kg/day for 5 consecutive days
- ☒ **Plasmapheresis**
- ☒ Other **immunosuppressive** drugs
- ☒ Chronic neuropathic pain: Gabapentin

## **Prognosis**

- Complete recovery in ≈ 85% starting within 2-3 weeks (in a **descending** manner)
- Residual weakness in some patients
- Chronic relapsing or unremitting GBS
- **Predictors** of poor prognosis
  - Cranial nerve involvement
  - Intubation
  - Maximum disability at presentation
- Complications & cause of death: Bulbar & respiratory muscle involvement

# Acute Paralysis

## Definition

Rapid loss of previously acquired motor skills (Over hours to days)

## Etiology

### A) Brain

- ☒ Stroke
- ☒ Trauma

### B) Brainstem

- ☒ Brainstem stroke
- ☒ Brainstem encephalitis

### C) Spinal cord

- ☒ Trauma
- ☒ Transverse myelitis

### D) AHC

- ☒ Poliomyelitis: Asymmetric Ascending paralysis
- ☒ Other enteroviruses

### E) Peripheral nerves

- ☒ Post-infectious Polyneuropathy (Guillain-Barre S): Symmetric Ascending paralysis
- ☒ Post-Diphtheritic paralysis: Symmetric-Descending
- ☒ Post-injectional paralysis: Monoplegia + radiating pain + Sciatic nerve\*
- ☒ Post-rabies vaccine
- ☒ Heavy metals
- ☒ Acute intermittent porphyria

### F) Neuromuscular

- ☒ Myasthenia gravis
- ☒ Botulism: Symmetric Descending paralysis
- ☒ Tick paralysis

### G) Muscles

- ☒ Hypokalemia
- ☒ Hypophosphatemia
- ☒ Periodic paralysis
- ☒ Trichinosis

## Clinical Evaluation

### A) Acute asymmetric:

### B) Acute symmetric:

### C) Pseudoparalysis: Trauma, fracture, Toxic synovitis of the hip, arthritis, osteomyelitis

# Limping Gait

## Etiology

### A) Unequal Limbs: Hemihypertrophy, Hemiatrophy, Shortening (Monoplegia, Poliomyelitis)

### B) Equal Limbs

Painful limp	Painless limp
Trauma, fracture	Monoplegia, Hemiplegia, CP
Osteomyelitis	Poliomyelitis
Arthritis	DDH
Toxic synovitis (Irritable hip)	Slipped upper femoral epiphysis
Malignancy	N/M disorder (Duchenne's)

# Autonomic Neuropathy

## Definition

- Affection of autonomic nerves
- It may be seen in many PN, however, some are **more** symptomatic (Autonomic neuropathy)

## Etiology

1. **Familial Dysautonomia**
2. **Congenital insensitivity to pain & anhidrosis**
3. **Hirschsprung disease**
4. **Reflex sympathetic dystrophy**
5. **Guillain-Barre Syndrome**
6. **Metabolic:** Fabry, Refsum disease, porphyria, DM
7. **Toxic** (*as before*)
8. **Infective:** Diphtheria
9. **Neoplastic:** Neuroblastoma, Lymphoma (*Paraneoplastic*)
10. **Horner syndrome**
  - Miosis
  - Ptosis (Partial)
  - Anhidrosis
  - Enophthalmos

Neuropathies

4



Note: Slight ptosis. Small but normally reacting pupil

## Autonomic Function Testing

Cardiac parasympathetic nervous system function	
HR variability (respiratory sinus arrhythmia)	
HR response to Valsalva	
HR response to standing	
Sympathetic adrenergic function	
BP response to Valsalva	
BP response to standing	
Sympathetic cholinergic function	
Thermoregulatory sweat testing	
Local axon reflex	

# **Familial Dysautonomia**

(Riley-Day Syndrome)

## **Etiology**

- AR<sup>9</sup>, common in Jews, 1:10,000, carrier rate = 1%

## **Pathology**

- ↓↓ No. of small unmyelinated nerve fibers (Pain, Temperature, taste, autonomic functions)
- ↓↓ No. of large myelinated nerve fibers (Deep sensation)

## **Clinical Picture** (Onset = Neonatal period)

### **A) Neonatal presentation**

- Feeding difficulties (poor suckling & swallowing)
- Hypotonia (**Floppy infant**)

### **B) Autonomic manifestation**

- Temperature instability: hypothermia & fever
- BP instability
- Failure to produce overflow tears (*normally at 2-3 months*)
- Corneal ulceration
- Sweating (hyperhidrosis)
- Bronchial secretion (pneumonia)

### **C) Sensory**

- Insensitivity to pain
- Deep sensory loss

### **D) CNS**

- Seizures
- Impaired intellectual functions

### **E) Autonomic crises:**

- Attacks of cyclic vomiting (every 20 min for 2-3 days) associated with HTN, sweating
- Gastric distension

## **Investigations**

- ECG: Long QT interval
- EEG: Seizures
- CXR: Infection
- ID histamine → Absent local axon reflex (No triple response)
- Denervation reactions
  - Noradrenaline (IV) → Exaggerated pressor response
  - Methacholine (IV) → Exaggerated hypotension
  - Methacholine (Eye drops) → Miosis
- ↓↓ Urinary VMA
- Genetic analysis: blood marker
- Autonomic Function Testing

## **Treatment**

- Eye protection (Methylcellulose eye drops)
- Nutritional & respiratory support
- Protection from injury (No pain)
- Anti-emetic (Chlorpromazine)
- Anti-epileptics
- Physiotherapy & Rx of scoliosis



# **Hirschsprung Disease**

(Aganglionic megacolon)

## **Pathology**

Absence of ganglionic cells from the myenteric & submucosal plexuses of rectum & variable distance of the colon

## **Clinical Picture**

A) **Neonatal period:** Delayed passage of meconium, IO, Hirschsprung's enterocolitis

B) **Childhood:** Chronic constipation

## **Investigations**

- Barium enema
- Anorectal manometry
- Suction rectal biopsy

## **PR examination in Hirschsprung**

- Narrow segment
- Gush of liquid stools & flatus

**Treatment** Surgical

# **Congenital Insensitivity to Pain & Anhidrosis**

- **Anhidrosis** (No sweating): Attacks of high fever (related to high environmental temperature)
- **Insensitivity to pain:** Frequent burns & skin injuries

# **Reflex Sympathetic Dystrophy**

**Etiology** Local trauma (contusion, laceration, fracture)

**Pathogenesis** Reflex over activity of autonomic nerves to injury

## **Clinical Picture**

- Acute state: Burning pain, hyperesthesia, erythema, sweating
- Chronic state: atrophy of muscle & skin

**Treatment** Physiotherapy, Sympathetic blockage or sympathectomy

# Congenital Myopathy

## Definition

Non-progressive, usually hereditary myopathies of variable severity (Benign ↔ Fatal)

**Myogenic Regulatory Genes** Family of 4 genes directs the striated muscle differentiation

## General Features

- Weakness/paralysis:
  - LMNL (Hypo-, hypo-, thin wasted muscles, ↓↓ fetal movements, poly-, arthrogryposis)
  - Bilateral, symmetrical, UL & LL, Proximal > Distal (**Floppy infant**)
- Variable severity
- Feeding difficulties (NGT)
- Respiratory paralysis (Suction, physiotherapy, M. ventilation)

## General Investigations

- CK, NCV, EMG, ECG are normal
- Muscle biopsy
- Genetic analysis

## General Treatment

- Supportive
- Respiratory & Nutritional support

Clinical Features of Congenital Myopathies				
Etiology	XLR	Sporadic	AD, AR	AD
Defect	Maturation arrest at the myotubular stage	Disturbed muscle fiber type differentiation		
Pathology	Centrally located nuclei ↑↑ Conc. of Desmin & Vimentin	Muscle fiber type 1 > Type 2	Rod-shaped structures within the muscle fibers	Central cores within the muscle fibers
C/P	Severe	<ul style="list-style-type: none"> <li>▪ Mild</li> <li>▪ Facies: Dolicocephaly, high-arched palate</li> <li>▪ Discrepancy between wasting &amp; weakness</li> </ul>	<b>A) Infantile form:</b> <ul style="list-style-type: none"> <li>▪ Severe</li> <li>▪ Facies: as CMFTD</li> </ul> <b>B) Juvenile form:</b> Mild	Malignant hyperthermia (100%)
Clinical Features of Congenital Myopathies				
Features	Brain Malformation ↓ Abnormal Descending impulses ↓ Abnormal Muscle development	<b>A) Single muscle:</b> <ul style="list-style-type: none"> <li>▪ Palmaris longus</li> <li>▪ Sternomastoid (Cong. torticoll)</li> </ul> <b>B) Group of muscles</b> <b>C) Generalized:</b> Fetal loss	Hypotonia ± Hyporeflexia No weakness No MR Recurrent joint dislocation [Diagnosis of exclusion]	<b>A) Idiopathic</b> <b>B) 2ry to neurogenic disease</b> <ul style="list-style-type: none"> <li>▪ SMA</li> </ul> <b>C) 2ry to myopathic disease</b> <ul style="list-style-type: none"> <li>▪ Congenital myopathy</li> <li>▪ Myotonic dystrophy</li> </ul>

# Muscular Dystrophy →

## Essential Criteria

- Primary myopathy
- Progressive

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- Genetic (XLR, AR; AD)
- Degeneration

- Duchenne
- Becker
- Emery-Dreifuss
- Limb girdle
- Facioscapulohumeral
- Congenital
- Myotonic

## Duchenne Muscular Dystrophy

### Incidence

- The most common hereditary N/M disease
- 1:3.600 liveborn ♂

### Etiology

- **XL-R** (*Locus dystrophin gene: Xp21*); 30% are new mutation
- Molecular defects: **Deletion**, duplication or point mutation at Xp21
- Dystrophin protein (important for Ca influx): expressed in muscles, heart, brain, retina
- Female carrier have no weakness but have ↑↑ CK "*Lyon hypothesis*"

### Pathology

- CT proliferation
- Myofibers (Degeneration & regeneration)
- Inflammatory cell infiltration
- Immunohistochemical staining: ↓↓ Dystrophin protein < 3 %

#### Pseudohypertrophy

1. Calf muscle
2. Tongue
3. Gluteus maximus
4. Quadriceps
5. Deltoid
6. Supra & infraspinatus

### Clinical Picture

A) **Infancy**: Asymptomatic or mild hypotonia

B) **Childhood**

- Skeletal Muscles**: Weakness at 3-5 yrs
  - LMNL (Hypo-, hypo-, **pseudohypertrophy**)
  - Bilateral, symmetrical, UL & LL, Proximal > Distal [Shoulder & pelvic girdles]
  - Respiratory & bulbar symptoms
  - Winging of the scapulae
  - Pot-belly abdomen
  - Exaggerated lumbar lordosis
  - Waddling gait
  - Gower's sign (Climbing rest: *hands pushing at the knees*)
  - Scoliosis & contractures (after loss of ambulation)
  - No affection of EOM, hand muscles or sphincters
- Cardiomyopathy** (50-80%)
- Intellectual Impairment** (25%)

#### Purely Motor

#### Proximal muscle weakness:

1. Climbing stairs
2. Combing hair
3. Gower's sign
4. Getting in & out of bed, chair or car

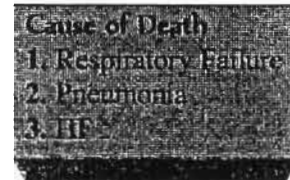
### Investigations

- Serum CK: Markedly ↑↑ (Thousands); even in presymptomatic
- AST & aldolase: ↑↑
- NCV: Normal
- EMG: Myopathic changes
- Muscle biopsy (Immunohistochemistry)
- CXR, ECG, Echo-
- Genetic analysis (PCR) & carrier detection: *False normal in 30%*
- Antenatal diagnosis (Fetal sex & genetic study)

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## Treatment (Supportive)

- Nutritional support & physiotherapy (avoid extensive physiotherapy)
- Orthopedic care: Lengthening of tendon Achilles
- Rx of complications: HF, chest infection...
- Steroids: 0.75 mg/Kg/day for the 1<sup>st</sup> 10 days of each month
- Myoblast transplantation (from the father, why??)
- Gene therapy & stem cell implantation



## Prognosis

- Wheelchair at 7-12 yrs
- Death before 20 yrs

# Becker Muscular Dystrophy

## As Duchenne but

- Onset: Later (Mean  $\approx$  12 yrs)
- Course: Slower (wheelchair  $\approx$  4<sup>th</sup> decade)
- Immunohistochemistry: Some dystrophin protein (20-90%)
- Intellectual impairment: Less
- Survival: More

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# Emery-Dreifuss Muscular Dystrophy

## Etiology

- XL-R: emerin gene  $\rightarrow$  Defective emerin protein

## Clinical Picture (Onset = Late childhood)

- Weakness: Scapulohumeroperoneal distribution...
- Cardiac manifestations: Arrhythmias & cardiomyopathy
- Normal mentality
- No hypertrophy

Cardiomyopathy

# Limb-Girdle Muscular Dystrophy

## Etiology AR

## Clinical Picture (Onset = Late childhood-adolescence)

- Shoulder & pelvic girdles (as in Duchenne)
- Normal heart & mentality
- Hypertrophy in some forms

# Facioscapulohumeral Muscular Dystrophy

(Landouzy-Dejerine Disease)

## Etiology

- AD
- Defective protein is sarcoglycan

## Clinical Picture (Onset = Early childhood)

- Facial muscles: Rounded mouth & failure of eye closure
- Shoulder girdle: Winging...
- Other muscles are then affected
- Asymmetry is common

Asymmetry

# **Congenital Muscular Dystrophy**

**Etiology** AR

**Clinical Picture** (Onset = Neonatal)

**Misleading term**

- Weakness (**Floppy infant**)
- Arthrogryposis is common

**Fukuyama Myopathy** is type of congenital muscular dystrophy (common in Japan)

## **Myotonic Muscular Dystrophy**

### **Myotonic Dystrophy**

**Incidence**

- The 2<sup>nd</sup> most common muscular dystrophy

**Triplet Repeat Expansion**

- ☒ Fragile X syndrome (XL-R)
- ☒ Huntington chorea (AD)
- ☒ Myotonic dystrophy (AD)

**Etiology**

- AD; two forms: DM1 (*Locus: 19q*), DM2 (*Locus: 3q*)
- It is caused by **Triplet Repeat Expansion** of (CTG)
- Expansion range from 50-2000 (Normal; 5-37); the larger, the worse
- If the gene is transmitted from the **mother** → severe congenital form (Imprinting)
- Tendency to have earlier onset &/or ↑↑ severity with successive generations (Anticipation)

**Clinical Picture**

**A) Neonatal form**

- Hypotonia (**Floppy infant**)
- Feeding & Respiratory complications
- ↓↓ Fetal movements & polyhydramnios

**Distal > Proximal**

**B) Infantile form**

- Facies: Concave temporalis, Inverted V-shaped upper lip & high-arched palate
- Cataract & frontal baldness
- Skeletal muscles: Weakness??
- Myotonia (= *Slow relaxation after muscle contraction*) develops after the age of 3 yrs
- Smooth muscles: GIT (Constipation), Uterus (↓↓ contractions)
- Cardiac: Heart block & arrhythmias (Not cardiomyopathy)
- Intellectual impairment
- Endocrinal: DM, delayed puberty, Adrenocortical insufficiency, Hypothyroidism
- Immunodeficiency

**Investigations**

- Serum CK: Normal (or mildly ↑↑)
- NCV: Normal
- EMG: Myotonic pattern
- ECG
- Genetic analysis & antenatal diagnosis

**Treatment** (Supportive)

- Myotonia: phenytoin & carbamazepine
- Physiotherapy
- Rx of complications: Cataract, Heart block...

# Myotonic Syndromes

## Myotonic Chondrodystrophy

(Schwartz-Jampel disease)

- Blepharophimosis
- Pursing of the mouth
- Puckering of the chin
- Phenotype & X-ray: Morquio-like
- Generalized muscle hypertrophy & weakness

## Myotonia Congenita

(Thomen disease)

- Chloride channelopathy (CLC1)
- Myotonia
- Generalized muscle hypertrophy
- Exercise ↓↓ myotonia & stiffness

## Paramyotonia Congenita

- Na channelopathy
- Exercise ↑↑ myotonia & stiffness
- Temperature-related myotonia: ↑↑ by cold & ↓↓ by warmth

XL-R	AR	AD
Duchenne	Limb-Girdle	Facioscapulohumeral
Becker	Congenital	Myotonic Dystrophy
Emery-Dreifuss		

## Triplet Repeat Expansion

<input checked="" type="checkbox"/> Duchenne's Muscular Dystrophy (XL-R)	<input checked="" type="checkbox"/> Spinocerebellar Ataxia
<input checked="" type="checkbox"/> Huntington's Chorea (AD)	<input checked="" type="checkbox"/> Friedreich's Ataxia
<input checked="" type="checkbox"/> Myotonic Dystrophy (AD)	<input checked="" type="checkbox"/> Sympathetic

## Endocrine Myopathy

### A) Thyroid:

- a. Hypothyroidism (Myxematous tissue)
- b. Hyperthyroidism
  - ☒ Thyroxin impairs muscle contractility
  - ☒ Myasthenia gravis

### B) Hyperparathyroidism (Fatigue overtone)

### C) Growth hormone

### D) Cushing (Steroid-induced myopathy)

- a. Exogenous (Cushinoid Syndrome)\*specially fluorinated steroids (Dexa-, Beta-)
- b. Endogenous (ACTH-dependent or non ACTH-dependent)

## Toxic Myopathy

1. **Inflammation:** Penicillamine, procainamide
2. **Necrosis:** Chloroquine, colchicine, cyclosporine, tacrolimus
3. **Rhabdomyolysis (Myoglobinuria):** Cocaine, alcohol, heroin, amphetamine
4. **Malignant hyperthermia:** Halothane, succinylcholine, ethylene, trichloroethylene
5. **Myotonia:** Cholesterol-lowering agents, chloroquine, cyclosporine
6. **Myosin loss:** Steroids

## Inflammatory Myopathy

↑↑ CK

### A) Dermatomyositis

- Skin: Heliotrope rash, V-sign, Gottron papules, Calcinosis, Partial baldness, Facial edema
- Muscle: Proximal muscle weakness

### B) Polymyositis: Rare

### C) Myositis in other diseases: JRA, SLE

### D) Viral myositis: Direct invasion or immune-mediated

### E) Parasitic myositis

- Trichinosis: Trichinella spiralis
- Toxoplasmosis

# Metabolic Myopathy

- K-related periodic paralysis
- GSD: 1, 2, 3, 5, 7
- Lipid Myopathies
- Malignant hyperthermia
- Mitochondrial
- Vitamin E Deficiency

## K-related periodic paralysis

### Etiology

- AD
- Mutations in genes encoding voltage-gated ion channels: sodium, calcium, and potassium
- **Hyperkalemic periodic paralysis:** Locus at 17q13.1-13.3
- **Hypokalemic periodic paralysis:** Locus at 1q31-32

### Clinical Picture

- Attacks of weakness or paralysis associated with hypo-\* or hyperkalemia
- Maximum weakness after awakening with gradual improvement over hours
- The usual frequency of attacks in childhood is once a week
- Normal in-between the attacks

### Investigations

Potassium level during the attack (ECG).

### Treatment

- **Hypokalemic type:** Oral potassium, low Na intake, acetazolamide, spironolactone

## Malignant hyperthermia

### Etiology

- Isolated AD (Locus: 19q, Ryanodine receptor)
- Associated with: Central core disease (100%), Duchenne...

### Pathogenesis

- Necrosis of muscle cell fibers in response to halothane or succinylcholine
- Rhabdomyolysis, myoglobinuria, ARF

Clinical Picture Attacks of extreme fever, muscle rigidity in response to...

Prevention Dantrolene sodium before anesthesia

### Investigations

- ↑↑ CK
- Myoglobinuria
- Muscle biopsy: Necrosis

## Glycogenosis (GSDs)

- GSD 1 (Von Gierke): G-6-Phosphatase
- GSD 2 (Pompe): Acid maltase
- GSD 3 (Cori): Debrancher
- GSD 5 (McArdle): Muscle phosphorylase
- GSD 7 (Tarui): Phosphofructokinase



# **Lipid Myopathy**

## **A) Primary carnitine deficiency**

**Defect** Defect in carnitine transporter in muscles, heart & kidneys

**Clinical Picture** Myopathy + Cardiomyopathy ± Nonketotic hypoglycemia

**Investigations** ↓↓ Serum carnitine + ↓↓ Tissue carnitine + ↑↑ Urine carnitine

**Treatment** Avoid fasting, ↓↓ Dietary long-chain FA, Carnitine supplementation

## **B) Secondary carnitine deficiency**

1. Organic acidemia
2. HD
3. Fanconi syndrome
4. Cystinosis
5. Valproate therapy

Carnitine is important in FA oxidation  
It acts as a carrier for long-chain FA

## **C) Muscle carnitine deficiency (AR)**

**Defect** Defect in carnitine transport across intestinal mucosa

**Clinical Picture** Myopathy + Cardiomyopathy

**Investigations** ↓↓ Muscle carnitine + Normal serum carnitine + Lipid vacuoles in biopsy

**Treatment** Avoid fasting, ↓↓ Dietary long-chain FA, Carnitine supplementation

## **D) Muscle carnitine palmitoyltransferase deficiency (CPT-II)**

**Defect** Deficiency in CPT-II enzyme

**Clinical Picture** Myopathy (as GSD 5 & 7) ± Nonketotic hypoglycemia

**Investigations** ↓↓ CPT-II

**Treatment** Avoid fasting, ↓↓ Dietary long-chain FA

# **Vitamin E Deficiency**

## **Etiology**

- Preterm (without supplementation)
- Malabsorption (Steatorrhea)

Vitamin E is antioxidant

## **Clinical Picture**

- ☒ Myopathy
- ☒ Neuropathy
- ☒ Hemolytic anemia

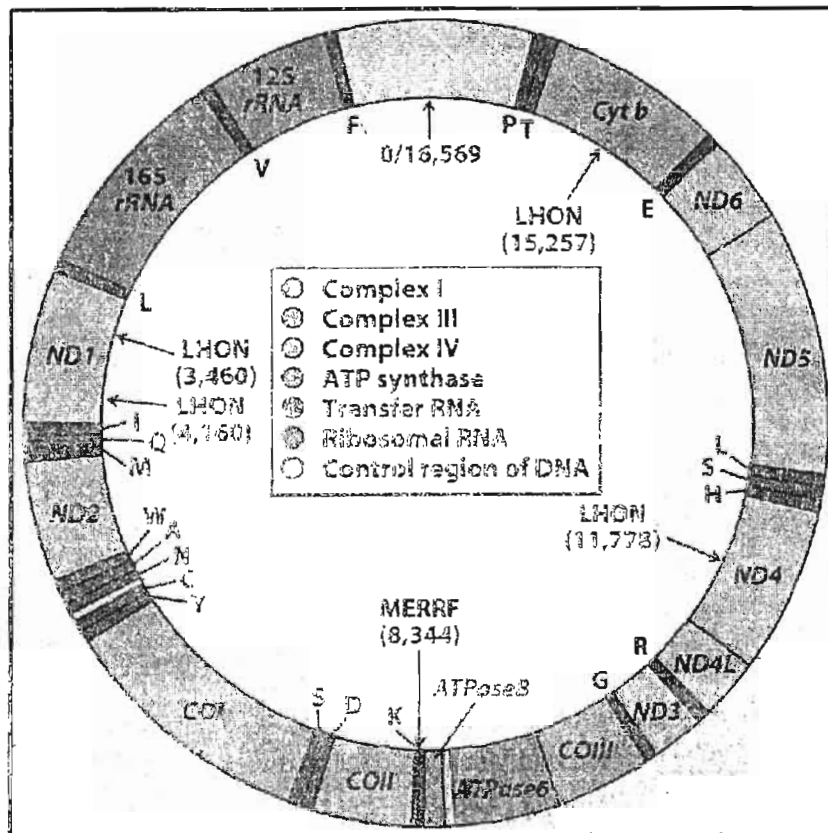
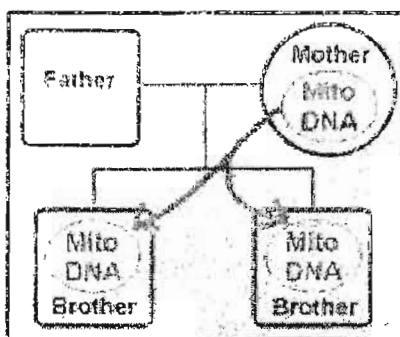
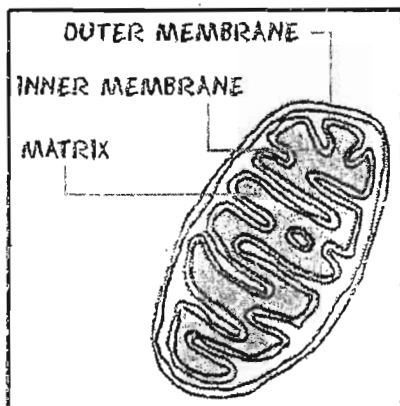
## **Treatment**

*Prophylactic* = 0.5-1.5 mg/d

*Therapeutic* = 5-30 mg/d [↑↑ PUFA → ↑↑ Vit.E requirements]

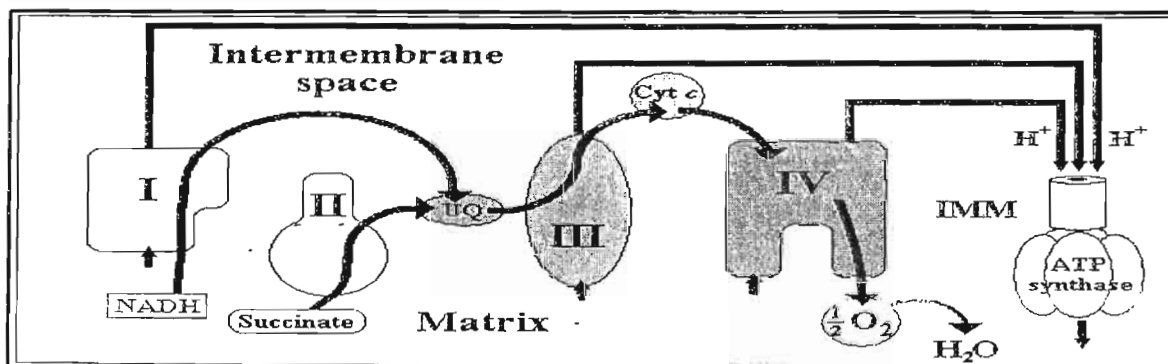
# Mitochondrial Diseases

## Mitochondrial Structure



## Mitochondrial DNA:

- The mitochondrion contains 2-10 copies of double stranded circular DNA (mt-DNA)
- Size  $\approx 16$  Kb
- No introns
- High mutation rate
- Exclusively transmitted by the mother [Sperm does not contain mitochondria]
- Slightly different genetic code (e.g., UGA codes for tryptophan not a stop codon)
- Mt-DNA codes for 13 proteins of the RC, 2 rRNA & 22 tRNA
- Proteins of the RC (85) are coded by mtDNA (74)\* & mtDNA (13)
- Homoplasmy: mtDNA is the same in all mitochondria (whether normal or mutant)
- Heteroplasmy: Mixture of normal & mutant mtDNA in different mitochondria
- Heteroplasmy can explain variable C/P with the same mtDNA mutation



# **Mitochondrial Diseases (& Myopathies)**

## **Definition**

Group of diseases related to dysfunction of mitochondria affecting various organs (↑↑ aerobic demand & ↓↓ regenerative capacity; CNS, muscles, heart & kidney)

## **Genetics**

Mutation in either nDNA or mtDNA

## **Clinical Picture**

- Multisystem affection of variable severity
- A newborn, infant, or young child with unexplained hypotonia, weakness, FTT & metabolic acidosis (particularly lactic acidosis)
- Each tissue can be affected alone (Pure mitochondrial myopathy, encephalopathy or cardiomyopathy) or more often in combination (Mitochondrial encephalomyopathy...)
- Clusters of symptoms & signs can be described as clinical syndrome (MELAS, MERRF)

### **a. Nervous system**

- Encephalopathy: recurrent or with low/moderate dosing of valproate
- Stroke-like events
- Ataxia
- Seizures
- Mental retardation
- Ocular: Ophthalmoplegia, ptosis, optic atrophy, pigmentary retinopathy
- Deafness

### **b. Muscles**

- Easy fatigability & exercise intolerance
- Weakness or paralysis

### **c. Heart:**

- Cardiomyopathy
- Conduction defects

### **d. Renal:** Tubular dysfunction: phosphaturia, aminoaciduria...

### **e. Liver:** Mitochondrial hepatopathy (Cholestasis, hepatomegaly, FHF)

**Genetically** Mitochondrial diseases can be divided into three groups:

- a. Defect in mtDNA (Maternal inheritance)
- b. Defect in nDNA
- c. Defect in communication between nDNA & mtDNA: disorders due to mutations in nuclear genes that control mitochondrial biogenesis

## **Investigations**

- **Metabolic acidosis**
- ↑↑ Serum & CSF lactate + ↑↑ Lactate/Pyruvate ratio
- **Muscle biopsy:** Ragged red fibers "Subsarcolemmal mitochondrial accumulation"
- Biochemical assay of RC complexes (By measuring of mitochondrial O<sub>2</sub> consumption)
- Investigations of the involved organs

## **Treatment** (No effective Rx)

- ↑↑ Dietary Carbohydrates
- Cocktails [Carnitine, Riboflavin, Coenzyme Q<sub>10</sub>, Vitamins C & E, thiamin, antioxidants]

# Mitochondrial Diseases

Disease	Mutation	Manifestations (&...)	Investigations
MELAS	- mtDNA point mutation (3243A>G) [A to G transition at position 3243]	<ul style="list-style-type: none"> <li>- Stroke-like events usually involving occipital, parietal &amp; posterior temporal lobes</li> <li>- Focal neurologic signs (recurrent hemiplegia/hemianopia)</li> <li>- Seizures, ataxia, dementia, recurrent migraine headache</li> <li>- Myopathy</li> <li>- Cortical blindness, vomiting</li> </ul>	<ul style="list-style-type: none"> <li>- Lactic acidosis</li> <li>- Muscle biopsy: RRF</li> <li>- CSF: ↑↑ proteins</li> <li>- SPECT: Regional hypoperfusion</li> <li>- MR spectroscopy: lactate peak</li> <li>- Complex I deficiency ± other complexes</li> </ul>
MERRF	- mtDNA point mutation	<ul style="list-style-type: none"> <li>- Progressive myoclonic epilepsy</li> <li>- Myopathy</li> <li>- Ataxia, seizures</li> </ul>	<ul style="list-style-type: none"> <li>- Lactic acidosis</li> <li>- Muscle biopsy: RRF</li> <li>- Complex II, III, IV deficiency</li> </ul>
NARP	- mtDNA point mutation	- Neuropathy, ataxia, retinitis pigmentosa	- No lactic acidosis - No RRF
LHON (Adult)	- mtDNA point mutation	<ul style="list-style-type: none"> <li>- Onset in the second or third decade of life</li> <li>- Optic atrophy (± Cardiac conduction abnormalities)</li> </ul>	
KSS	- mtDNA deletion	<ul style="list-style-type: none"> <li>- Triad of [Onset &lt; 20 yrs, PEO, Pigmentary retinopathy] +</li> <li>- One of [Heart block, Ataxia, CSF proteins &gt; 100 mg%]</li> <li>- Endocrinal: DM, hypoparathyroidism, short stature</li> <li>- Sensorineural deafness</li> </ul>	
CPEO	- mtDNA deletion	- PEO, ptosis (± Myopathy)	
Pearson	- mtDNA deletion	- Sideroblastic anaemia & Pancreatic insufficiency	
Leigh disease (Infancy)	- Nuclear: SURF1 gene	<ul style="list-style-type: none"> <li>- Hypotonia, feeding problems, FTT, developmental delay</li> <li>- Seizures, ataxia, intermittent respiration with ↑↑ sighing</li> <li>- External ophthalmoplegia, ptosis</li> </ul>	<ul style="list-style-type: none"> <li>- Lactic acidosis</li> <li>- CT &amp; MRI: Bilateral symmetric areas of low attenuation in the BG &amp; brainstem</li> <li>- MR spectroscopy: lactate peak</li> <li>- Pathology: necrosis &amp; cystic changes</li> </ul>
Other causes of mit. myopathy		Cytochrome-c oxidase deficiency, Coenzyme Q10 deficiency	

**Leigh syndrome** (Subacute necrotizing encephalomyopathy): **Most common** mitochondrial encephalomyopathy in infancy & childhood (Many die < 1.5 yr)

Leigh syndrome may be due to: Pyruvate dehydrogenase complex deficiency, Complex I, II, IV or V deficiency or Coenzyme Q10 deficiency

CPEO: Chronic progressive external ophthalmoplegia LHON: Leber's hereditary optic neuropathy NARP: Neuropathy, ataxia and retinitis pigmentosa

# Increased Intracranial Pressure

## Definition

Increased ICP (Normal pressure = 0-15 mmHg or 0-200 mm H<sub>2</sub>O)  
Clinical manifestations of ↑↑ ICP occurs when pressure > 25 mmHg

## Etiology

### A) Brain edema

	1. Cytotoxic*	2. Vasogenic	3. Interstitial
Type	Intracellular edema	Extracellular edema	Extracellular edema
Mechanism	Cellular damage	↑↑ capillary permeability	↑↑ CSF pressure
Site	Grey matter	White matter	White matter
Causes	<ul style="list-style-type: none"> <li>▪ CNS infection</li> <li>▪ Trauma</li> <li>▪ HIE</li> <li>▪ Met. encephalopathy</li> </ul>	<ul style="list-style-type: none"> <li>▪ CNS infection</li> <li>▪ Around pathological masses</li> </ul>	Hydrocephalus
Response to Rx	Poor	Relatively Good	Relatively Good

### B) ↑↑ Cerebral blood flow

1. Hypertension
2. Hypercapnia & Hypoxemia
3. Hyperpyrexia
4. Convulsions

### C) ↑↑ CSF volume

1. ↓↓ CSF absorption (obstructive & communicating hydrocephalus)
2. ↑↑ CSF production

### D) Pathological masses

1. Abscess & tumor
2. Intracranial hemorrhage

## Clinical Picture

### A) Bulging anterior fontanel: Useful in neonates & infants

### B) Papilledema

### C) Nonspecific

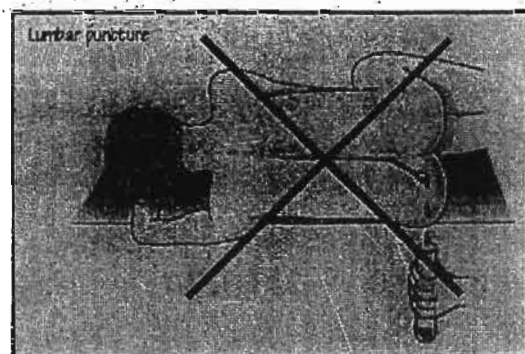
- Headache, vomiting & blurring of vision
- Cushing response (Bradycardia + Hypertension)

### D) Neurological

- Disturbed conscious level (degree??)
- Hypertonia
- Hyperreflexia
- Hyperventilation
- Sluggish papillary reaction

### E) Marked ↑↑ ICP

- Cerebral ischemia
- Convulsions
- Herniation syndromes
  - Central transtentorial: Rostral-to-caudal deterioration (Detected clinically by the change of motor response from flexion withdrawal to decorticate or decerebrate extension)
  - Uncal: Unilateral dilated irreactive pupil (3<sup>rd</sup> nerve palsy)
  - Cerebellar tonsils: Neck rigidity
  - Medullary herniation: occurs if lumbar puncture is done with a markedly ↑↑ ICP  
[Apnea, Hypotension, Hypotonia]



## **Investigations**

- CT Brain
  - Pathological masses
  - Loss of CSF spaces
  - Type (Grey or white matter edema)
- Measurement of ICP
  - Intraventricular catheter
  - Epidural catheter
  - External monitor via anterior fontanel

## **Treatment**

### **A) Rapidly-acting measures**

- ☒ Head elevation (30°)
  - ↑↑ VR from the brain
  - Avoid higher elevation & head tilt (neutral position)
- ☒ Hyperventilation
  - ↓↓ CO<sub>2</sub> to 25-35 mmHg (↓↓ Cerebral blood flow)
  - ETT + Mechanical ventilation (PEEP should not be > 3-4 mmHg, why?)
- ☒ Mannitol 20%
  - Mechanism: Cell dehydration + Diuretic effect
  - Dose: 0.5-1 g/Kg/dose every 6 hrs for a maximum of 2 days

### **B) Slowly-acting measures**

- ☒ Fluid restriction (60-70% of maintenance)
- ☒ Furosemide
  - Mechanism: Prevention of fluid accumulation + Diuretic effect
  - Dose: 0.5-1 mg/Kg/dose over 30 minutes every 4-6 hrs
- ☒ Steroids (Dexamethasone)
  - Mechanism: Prevention of fluid accumulation (Anti-inflammatory)
  - Dose: 0.25 mg/Kg/dose every 6-12 hrs for a maximum of 2 days
  - Useful only in vasogenic edema

### **C) Other measures**

- ☒ Rx of hyperpyrexia & convulsions
- ☒ Rx of hydrocephalus
- ☒ Removal of pathological masses (abscess & tumor)

# Brain Tumors

## Incidence

- The 2<sup>nd</sup> most common malignancy in children
- Peak age: 5-10 yrs

## Predisposing Factors

- Neurocutaneous syndromes →
- Immunodeficiency syndromes: Ataxia telangiectasia

### Neurocutaneous syndromes

- ☒ Neurofibromatosis
- ☒ Tuberous sclerosis
- ☒ Von-Hippel-Lindau

## Classification

A) Infratentorial tumors (Posterior fossa tumors)	↑↑ ICP &/or Ataxia
B) Supratentorial tumors	Focal neurological signs &/or Endocrinal

## Clinical Picture

### A) ↑↑ Intracranial pressure (± Herniation)

- ☒ **Infancy:** Bulging AF, progressive head enlargement
- ☒ **Older children:** Headache, vomiting & blurring of vision
  - Headache: Morning, Dull-aching, generalized, ↑↑ with coughing & straining up, ↓↓ with standing & vomiting
  - Vomiting: Projectile, not related to meals, not preceded by nausea
  - Blurring of vision

### Causes of ↑↑ ICP

- ☒ Tumor
- ☒ Hge in the tumor
- ☒ # CSF & # VR

### B) False localizing signs

- ☒ 6<sup>th</sup> nerve palsy (Convergent squint)
- ☒ Changes in personality, mentality & speech

### C) True localizing signs

- ☒ **Frontal lobe**
  - Hemiplegia & mentality changes
  - Focal seizures
- ☒ **Parietal lobe**
  - Cortical sensory loss
  - Sensory seizures
- ☒ **Temporal lobe**
  - Auditory agnosia
  - Focal seizures
- ☒ **Occipital lobe**
  - Contralateral homonymous hemianopia
  - Visual hallucination
- ☒ **Cerebellar Ataxia**
- ☒ **Cranial nerve affection**
- ☒ **Pituitary tumors (Craniopharyngioma)**
  - Hormonal manifestations:
    - Gigantism, acromegaly & Cushing's syndrome
    - Hypopituitarism
  - Compression manifestations:
    - Optic nerve: Ipsilateral visual loss
    - Optic chiasma: Bitemporal hemianopia
    - Optic tract: Contralateral homonymous hemianopia
    - Hypothalamus →

Brain tumors should be excluded in any child with Ataxia

### Hypothalamic syndrome

- Hypo-, hyperthermia
- Adipsia, Diabetes insipidus
- Obesity, cachexia
- Hypersomnia
- Gelastic seizures

## Infratentorial tumors (Posterior fossa tumors)

Incidence	Most common post. fossa tumor	Next most common
Consistency	Usually cystic	Usually solid
Site	Usually unilateral One cerebellar hemisphere	Usually midline Both hemispheres
Metastases	No	Extracranial sites & seedling
Growth	Slowly growing	Rapidly growing
C/P	Ipsilateral ataxia + ↑↑ ICP	Ataxia + ↑↑ ICP ( <i>more rapid</i> )
Rx	Surgery + Radiotherapy	Surgery + Radiotherapy + Chemo-
Prognosis	5-yr survival = 90%	5-yr survival = 60%

### Brain Stem glioma

- ☒ 3<sup>rd</sup> Most common posterior fossa tumor
- ☒ C/P: Crossed hemiplegia (Ipsilateral cranial nerve palsy + Contra lateral hemiplegia)
- ☒ Rx: Radiotherapy
- ☒ Prognosis: Poor

### Ependymoma

- ☒ Arises from the ependymal lining of the 4<sup>th</sup> ventricle
- ☒ C/P: ↑↑ ICP (Early obstruction of CSF flow) without ataxia
- ☒ Rx: Surgery + Radiotherapy

## Supratentorial tumors

### Craniopharyngioma

- ☒ Most common supratentorial tumor (remnants of embryonic Rathke's pouch)
- ☒ Consists of solid & cystic areas
- ☒ Calcification is common
- ☒ C/P: Focal neurological signs (Visual??), Endocrinal (DI), ↑↑ ICP
- ☒ Rx: Surgery ± Radiotherapy

### Cerebral Astrocytoma

- ☒ It is the most common brain tumor (low-grade or high-grade)
- ☒ C/P: Focal neurological signs
- ☒ Rx: Surgery + Radiotherapy

### Optic Glioma Focal neurological signs (Visual)

### Pineal region tumors ↑↑ ICP, Precocious puberty

Pineal region tumors

### Choroid plexus papilloma Hydrocephalus "↑↑ CSF production" (Lateral ventricle\*)

### Leukemia Focal neurological signs

### Diagnosis

1. Clinical suspicion
2. Lab: Hormonal assay
3. Imaging: Cranial US, Skull X-rays, CT, MRI



# **Pseudotumor Cerebri**

(Idiopathic intracranial hypertension)

## **Definition**

Increased ICP without any evidence of intracranial mass lesion or ventricular dilatation

## **Pathogenesis**

- ☒ Alteration in CSF production & absorption
- ☒ Alteration in cerebral blood flow & venous return

## **Etiology**

### **A) Metabolic:**

- Hypervitaminosis A & Vitamin A deficiency
- Hypoparathyroidism & pseudohypoparathyroidism
- Addison disease
- Prolonged steroid therapy (& rapid withdrawal)
- Obesity & pregnancy
- Refeeding syndrome
- Galactosemia

### **B) Infection:** Roseola, measles, GBS, chronic OM, mastoiditis, sinusitis, tonsillitis

### **C) Hematological**

- Polycythemia
- Anemia (hemolytic & iron deficiency)
- Wiskott-Aldrich syndrome

### **D) Venous obstruction**

- Lateral sinus or posterior sagittal sinus thrombosis

### **E) Drugs:** Steroids, nitrofurantoin, tetracycline, GH, OCPs

### **F) Idiopathic**

**Diagnosis of Exclusion**

## **Clinical Picture**

- ↑↑ ICP (Headache, vomiting, blurring of vision, bulging AF ...)
- Ophthalmological examination: Papilledema with ↑↑ Blind spot
- No focal neurological signs
- Optic atrophy in prolonged untreated patients "Not benign"

## **Investigations**

- Imaging (CT & MRI)
  - Normal ventricular size, anatomy & position
  - No focal lesions
- Ophthalmologic evaluation: VA, fundus, visual-evoked potentials
- Lumbar puncture: Diagnostic & therapeutic (Normal pressure = 0-15 mmHg or 0-200cm H<sub>2</sub>O)

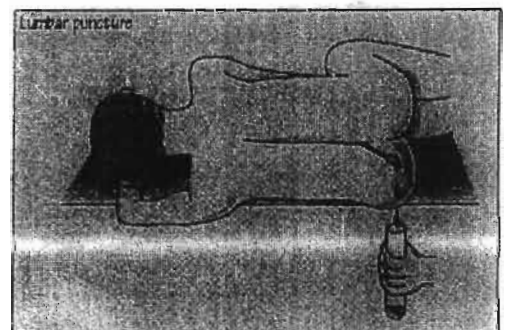
**Imaging & re-imaging is needed to exclude small brain tumors**

## **Treatment**

1. Rx of the underlying cause...
2. Close F/U (Field of vision & fundus examination)
3. Acetazolamide (10-30 mg/Kg/day): ↓↓ CSF production
4. Repeated lumbar puncture
5. Lumboperitoneal shunt

## **Prognosis**

- Spontaneous resolution-
- Optic atrophy & blindness



# Neurocutaneous Syndromes

## Definition

They are a group of disorders characterized by involvement of the CNS & skin (Integument)

## Neurofibromatosis

### Classification

- NF type 1: AD<sup>17</sup>. It is the most common neurocutaneous syndrome (1:3.000)
- NF type 2: AD<sup>22</sup>. Central type (why?), 1:25.000

### Neurofibromatosis Type 1

#### Diagnostic Criteria

1. **Café-au-lait patches** (100% of patients)
  - Prepubertal:  $\geq 6$  macules; 5 mm in diameter
  - Postpubertal:  $\geq 6$  macules; 15 mm in diameter
2. **Axillary freckling**: Hyperpigmented areas
3.  $\geq 2$  **Iris Lisch nodules** (Hamartomas)
4.  $\geq 2$  **neurofibroma** or 1 **plexiform neurofibroma**
5. **Osseous lesions** (e.g., sphenoid dysplasia, kyphoscoliosis)
6. **Optic glioma** (VA & visual field defects)
7. **1<sup>st</sup> degree relative with NF-1**

DD of café-au-lait spots:

1. Neurofibromatosis
2. Fanconi anemia
3. McCune Albright
4. Chediak-Higashi
5. Ataxia telangiectasia
6. Bloom
7. Tuberous sclerosis

2/7

#### Complications

- |   |                       |
|---|-----------------------|
| 1. Learning disabilities (30%)                  | 5. Hypertension, why? |
| 2. Seizures (8%)                                | 6. Precocious puberty |
| 3. Hydrocephalus                                | 7. Scoliosis          |
| 4. $\uparrow\uparrow$ Incidence of brain tumors | 8. Psychological      |

Genetics New mutation in > 50%, prenatal diagnosis is available

### Neurofibromatosis Type 2

#### Diagnostic Criteria

1. **Bilateral acoustic neuromas** (8<sup>th</sup> nerve schwannoma)
2. **Unilateral acoustic neuroma + parent or sibling with NF-2**
3. **Unilateral acoustic neuroma + any 2 of** (meningioma, schwannoma, glioma, neurofibroma, posterior lenticular opacities)
4. **Unilateral acoustic neuroma + multiple meningiomas**

1/4

## Von-Hippel-Lindau Disease

### Etiology

AD (1:36.000)

### Clinical Picture

1. **Neurological**
  - Cerebellar hemangioblastoma: Cerebellar ataxia
  - Spinal cord hemangioblastoma: Sensory ataxia
2. **Retinal angiomas**: Treated by photocoagulation or cryotherapy
3.  $\uparrow\uparrow$  incidence of tumors: Pheochromocytoma
4. **Cystic lesions**: Kidneys, liver, pancreas

Renal carcinoma is the main cause of death

# Tuberous Sclerosis

## Etiology

- AD (1:6.000)
- Two genes: TSC1 (Chromosome 9) & TSC2 (Chromosome 16) coding hamartin & tubulin
- TSC genes are tumor suppressor genes
- New mutation in 2/3 of cases, prenatal diagnosis is available
- Multisystem disease

**TS Complex**

## Pathology

- Cerebral cortical tubercles
- Subependymal tubers that may become calcified [Candle-dripping appearance]
- These tubers may grow into subependymal giant cell astrocytomas (SEGAs)

## Clinical Picture

### 1. Neurological

- Convulsions (Infantile spasm\*, myoclonic epilepsy...)
- Mental retardation (60-70 %)
- Behavioral abnormalities (e.g., autism, rage...)

**Any type of convulsions except petit mal**

### 2. Skin manifestations

- Hypopigmented macules ( $\geq 3$ ): Earliest
- Adenoma sebaceum (Facial angiofibromas): nose & cheeks
- Shagreen patches: rough raised lesions with orange-peel surface (Lumbosacral area)
- Fibrous forehead plaque
- Periungual fibroma

**DD: acne**

### 3. ↑↑ Incidence of brain tumors

### 4. Hydrocephalus

### 5. Heart (50%): Rhabdomyoma (slow spontaneous resolution is common!)

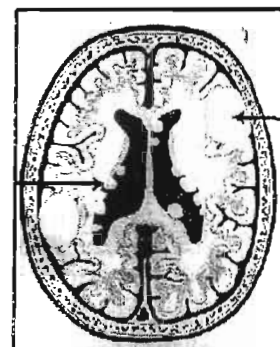
### 6. Renal angiomyolipoma & renal cysts

### 7. Pulmonary lymphangiomyomatosis

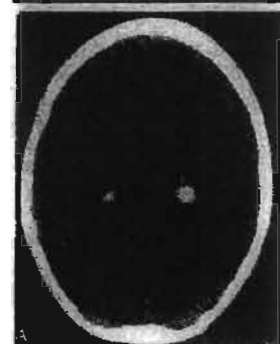
**Renal failure is the main cause of death**

## Criteria of TSC

Major Features	Minor Features
Cortical tuber	Cerebral white matter migration lines
Subependymal nodule	Multiple dental pits
SEGAs	Gingival fibromas
Adenoma sebaceum or forehead plaque	Bone cysts
Periungual fibroma	Retinal achromatic patch
Hypomelanotic macules ( $>3$ )	Confetti skin lesions
Shagreen patch	Nonrenal hamartomas
Multiple retinal hamartomas	Multiple renal cysts
Cardiac rhabdomyoma	Hamartomatous rectal polyps
Renal angiomyolipoma	
Pulmonary lymphangiomyomatosis	



**2 major or 1 major + 2 minor**



**Follow-up** Brain MRA (every 1-3 yrs), renal imaging (every 1-3 yrs)

# Sturge-Weber Disease

## Etiology

Sporadic (1:50,000)

## Pathology

- Abnormal cerebral vascularization (↑↑ vascularization of the leptomeninges)
- Pressure atrophy of the underlying brain tissue

## Clinical Picture

1. Neurological
  - Convulsions (*Contralateral side*)
  - Hemiplegia/paresis
  - Learning disabilities (50%)
2. Skin manifestations: Facial nevus (port-wine stain)
3. Glaucoma & buphthalmos (*Ipsilateral*)

Not all individuals with port-wine stain have SWS

Always involves the upper face but may involve lower face & trunk

## Investigations

- Skull X-ray: Serpentine appearance (occipitoparietal region)
- Brain CT & MRI

# Incontinentia pigmenti

Etiology XL-D (Lethal in most, but not all, males)

## Clinical Picture

1. Neurological: Seizures, mental retardation
2. Skin manifestations: The skin lesions evolve through 4 characteristic stages:
  - a. Blistering (Birth-4 months)
  - b. Wart-like rash (for several months)
  - c. Swirling macular hyperpigmentation (6 months-adulthood)
  - d. Linear hypopigmentation
3. Ocular: neovascularization, microphthalmos, squint, optic nerve atrophy, cataracts
4. Others: Alopecia, abnormal tooth shape, dystrophic nails & skeletal defects

# Hypomelanosis of Ito

(Incontinentia pigmenti achromians)

## Definition

It is a cutaneous condition characterized by various patterns of bilateral or unilateral hypopigmentation following Blaschko's lines (*Invisible skin lines*)

# PHACE Syndrome

Posterior fossa malformations, Hemangioma, Arterial anomalies, Coarctation, Eye anomalies

# Linear Nevus Syndrome

Mental retardation & seizures + Facial nevus (forehead)

# Ataxia telangiectasia

# Refsum Disease

# Pediatric Stroke Syndrome

## Definition of Stroke

Rapidly developing signs of focal brain dysfunction with symptoms lasting for  $\geq 24$  hrs with no apparent cause other than of vascular origin

## Classification of Stroke

1. Arterial ischemic stroke (AIS)
2. Cerebral sinovenous thrombosis (CSVT)
3. Hemorrhagic stroke (HS)

## Hemiplegia

### Definition

Weakness or paralysis of one side of the body due to pyramidal tract lesion at any point from its origin in the cerebral cortex down to the 5<sup>th</sup> cervical segments (origin of brachial plexus)  
 ➡ 3 levels [Spinal cord, brain stem & cerebral]

### Etiology

1. Stroke
2. CNS Infection: Meningitis, encephalitis
3. Cerebral palsy: Hemiplegic CP
4. Neoplastic: Brain tumors
5. Degenerative: Multiple sclerosis
6. Todd's paralysis
7. Metabolic: MELAS, homocystinuria, Fabry, OTC deficiency, hyperlipidemia
8. Migraine: Hemiplegic migraine
9. Hematological: Sickle cell...
10. Hysterical

### Clinical Picture (Classical C/P)

- Onset & Course: Acute & regressive (vascular) or gradual & progressive (neoplastic)
- Acute cases pass into 2 stages of paralysis (Shock stage & spastic stage)
- Chronic cases pass directly into the spastic stage

#### A) Shock stage

- Weakness or paralysis
  - Hypotonia & hyporeflexia + (+ve Babinski sign)
  - One side of the body
- Duration: 2-6 wks

#### B) Stage of spastic paralysis

- Weakness or paralysis
  - One side of the body, Distal > Proximal
  - Paralysis is more in the Progravity muscles
  - Hypertonia (Spasticity) is more in the antigravity muscles
  - Hyperreflexia, pathological reflexes (Finger, patellar, adductor reflexes)
  - Clonus (wrist, ankle, patellar)
  - +Ve Babinski sign
- Gait: Circumduction

#### • Antigravity muscles

- UL flexors
- LL extensors

#### • Progravity muscles

- UL extensors
- LL flexors

## Spinal Cord (= Brown-Sequard syndrome)

### Site of the Lesion

Hemisection of the spinal cord (C1-C5)

### Clinical Picture

#### a. At the level (*Root affection*)

- ☒ **Motor:** Ipsilateral paralysis of the muscles supplied by the affected segments...
- ☒ **Sensory:** Ipsilateral loss of all sensations in the area supplied by the affected segments

#### b. Below the level

- ☒ **Motor:** Ipsilateral hemiplegia
- ☒ **Sensory:**
  - Ipsilateral deep sensory loss
  - Contralateral loss of pain & touch sensation
  - ↓↓ Touch on both sides

## Brain Stem

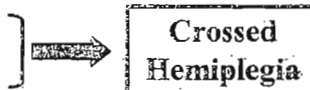
### Site of the Lesion

One side of the brain stem

### Clinical Picture

#### a. At the level: Ipsilateral cranial nerve affection (LMN nature)

#### b. Below the level: Contralateral hemiplegia (UMN nature)



### Examples

- ☒ **Midbrain (Weber syndrome):** 3<sup>rd</sup> cranial nerve
- ☒ **Pons: (Millard-Gubler syndrome):** 6<sup>th</sup> & 7<sup>th</sup> cranial nerves
- ☒ **Medulla: (Jackson syndrome):** 11<sup>th</sup> & 12<sup>th</sup> cranial nerves

## Cerebral

### Site of the Lesion

Lesion in the cerebral hemisphere (cortical, subcortical or capsular)

### Clinical Picture

- a. Contralateral Hemiplegia
- b. Contralateral paralysis of VII & XII nerves

### Level

	Cortical	Subcortical	Capsular
<b>Features</b>	Coma Convulsions Aphasia (dominant hemisphere)	The same as cortical	No Coma No Convulsions No Aphasia
<b>Extent</b>	Usually monoplegia (incomplete) Hemihyposthesia (parietal lobe)	More extensive	Complete hemiplegia Hemihyposthesia

### Investigations (*According to the clinical suspicion*)

- Imaging (CT & MRI)
- Investigation of the cause: CBC, bleeding profile, metabolic screening, Hb electrophoresis
- ECG, Echocardiography, Doppler, MRA, Angiography

### Treatment

A) Care of the comatose

Diagnosis of Hemiplegia??

## B) Specific management

### Stroke-Like Events:

#### Definition

All non-vascular causes of hemiplegia

#### Etiology

1. **Migraine**
  - Aura
  - Specially certain types of migraine: Hemiplegic migraine, aura without headache
2. **Seizures**
  - Todd paralysis
3. **Infection**
  - Meningitis & encephalitis
4. **Demyelination**
  - Gradual (Hours-days)
  - ADEM is multifocal
5. **Hypoglycemia**
  - Predisposing factors: IDDM, adrenal insufficiency, steroid withdrawal
6. **Global HIE**
  - Decreased cerebral perfusion (Sepsis, HF, dehydration)
7. **Hypertensive encephalopathy**
8. **Inborn errors of metabolism**
  - MELAS is the classical example
  - Fabry & homocystinuria: True ischemic stroke
9. **Vestibulopathy/ataxia**
  - Cerebellar ataxia, vestibular neuronopathy, viral labyrinthitis, benign paroxysmal vertigo
10. **Channelopathies**

# Paraplegia

## Definition

Weakness or paralysis of both LL

- a. **Spastic paraplegia\***: Bilateral pyramidal tract affection (Cerebral or spinal) = UMN
- b. **Flaccid paraplegia**: Cauda equina lesions & PN = LMN

## Etiology

### Clinical Picture (Spastic paraplegia)

a. At the level (**Root affection**) "Only in extramedullary lesions"

- ☒ **Motor**: Ipsilateral paralysis of the muscles supplied by the affected segments...
- ☒ **Sensory**: Ipsilateral loss of all sensations in the area supplied by the affected segments
- ☒ **Pain**: in vertebral lesions

b. Below the level

☒ **Motor**: Paraplegia

- Both LL, Distal > Proximal
- Paralysis is more in the progravity muscles
- Hypertonia (Spasticity) is more in the antigravity muscles
- Hyperreflexia, pathological reflexes (Patellar & adductor reflexes)
- Clonus (Ankle, patellar)
- +ve Babinski sign

☒ **Sensory & sphincteric**:

▪ Extramedullary lesions: Sensory level below which, all sensation are lost

Early loss of sensation in the saddle area

Late bladder disturbances

▪ Intramedullary lesions: Jacket sensory loss of dissociated nature (Pain & Temp.)

Sacral spare

Early bladder disturbances

- Acute cases: Shock & spastic stages
- Chronic cases: Spastic stage

### Investigations (According to the clinical suspicion)

- Imaging (CT & MRI)
- X-ray spine
- Investigation of the cause: CBC, NCV, EMG, MRA, Angiography

### Treatment

A) Care of the comatose

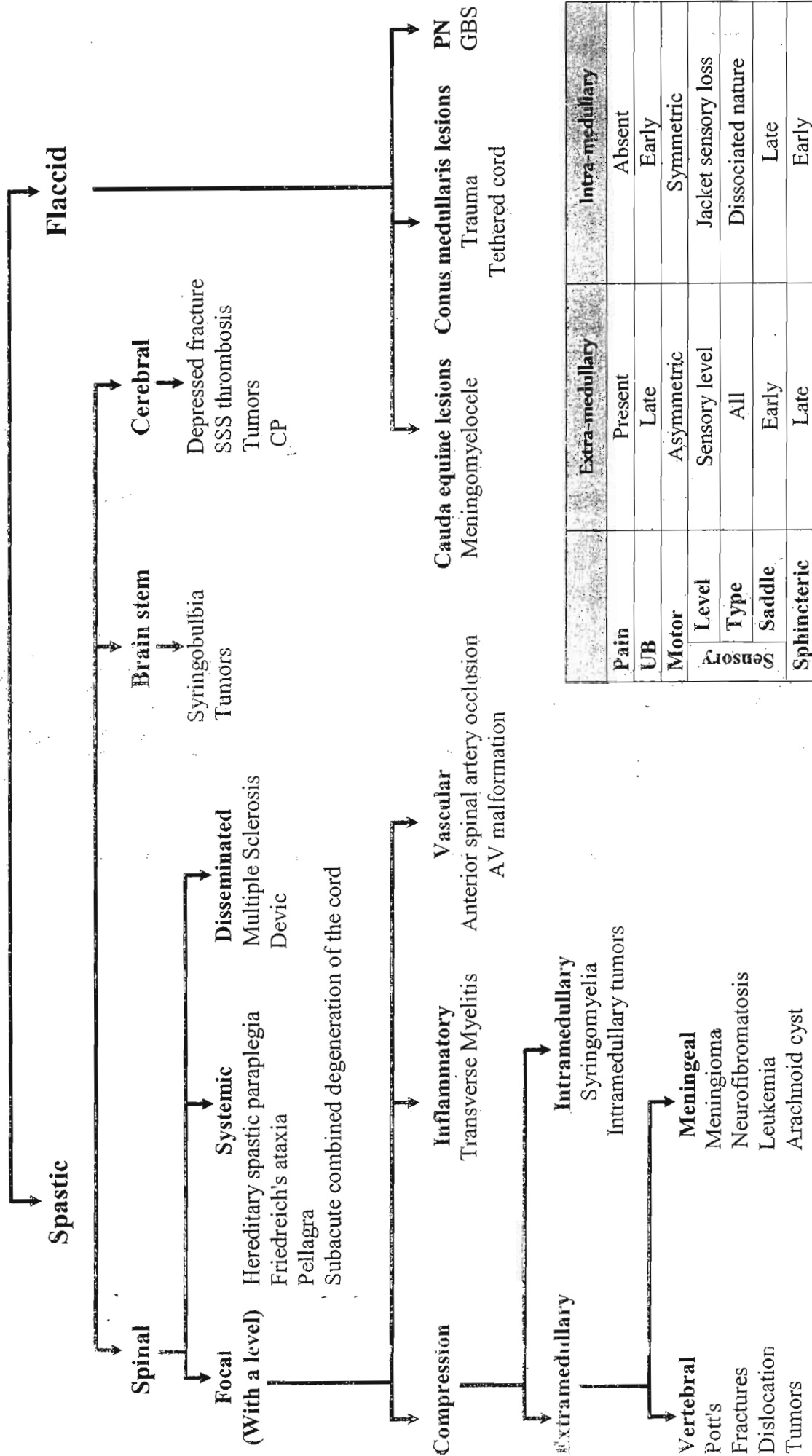
B) Specific management

- ☒ TB
- ☒ Neoplasm
- ☒ CP

<b>Tone</b>	Hypotonia	Hypertonia
<b>Reflexes</b>	Hyporeflexia	Hyperreflexia
<b>Pathological Reflexes</b>	Absent	May be present
<b>Clonus</b>	Absent	May be present
<b>Sensation</b>	Intact ولكن	Lost (Level)
<b>Plantar Reflex</b>	Equivocal	Positive



# Paraplegia



# Neurodegenerative Disorders

Usually fatal

## Definition

**Heterogeneous** group of diseases characterized by **regression & progressive deterioration** of previously acquired neurologic functions (Intellectual, motor, sensory) with loss of speech, vision & hearing, often associated with seizures & feeding difficulties

## Classification

A) **Gray matter diseases** [Early manifestations = Seizures, visual & intellectual]

### a. Storage diseases

- GM1 Gangliosidosis
- GM2 Gangliosidosis
  - Tay-Sachs
  - Sandhoff
- Gaucher
- Niemann-Pick
- Neuronal ceroid lipofuscinoses

Disease		Enzyme Defect
Gaucher		$\beta$ -Glucocerebrosidase
Niemann-Pick		Sphingomyelinase
GM <sub>1</sub> Gangliosidosis		$\beta$ -Galactosidase
GM <sub>2</sub>	Tay-Sachs	Hexosaminidase A
	Sandhoff	Hexosaminidase A & B
NC lipofuscinoses		Palmitoyl-protein thioesterase

### b. Non-storage diseases

- Leigh disease
- Other mitochondrial diseases

B) **White matter diseases** [Early manifestations = Motor dysfunction, hypotonia, spasticity]

### a. Leukodystrophies (Loss of...)

Disease	Genetics	Main Clinical manifestations
Canavan		Macrocephaly
Alexander		Macrocephaly
Metachromatic LD		Regression & ataxia
Krabbe disease		Spasticity, $\uparrow\uparrow$ irritability & $\uparrow\uparrow$ crying
Kinky hair disease		Hypotonia, seizures
Neonatal ALD		Hypotonia, seizures
XL ALD		Onset = 3-4 yrs (academic $\downarrow\downarrow$ , seizures, spasticity)

### b. Demyelinating diseases (Loss of...): MS

C) **Other degenerative brain diseases:**

- Friedreich's ataxia
- Ataxia telangiectasia
- Abetalipoproteinemia (Acanthocytosis)
- Huntington chorea
- Wilson disease
- Idiopathic torsion dystonia
- Hallervorden-Spatz
- Subacute sclerosing panencephalitis

## Investigations

- In the past: Brain & rectal biopsy
- Now: Neuroimaging (MRI), biochemical (Enzyme) & molecular genetics

## Prevention

- Antenatal diagnosis (Amniocentesis & CVS)
- Carrier detection (Enzyme assay)

**Prognosis** Usually fatal

# Sphingolipidosis

## Definition

- Group of diseases characterized by accumulation of sphingolipids
- Sphingolipids: Sphingosine-containing lipids (*Cerebrosides, gangliosides*)
- Sphingosine is an amino alcohol

## **Sphingolipidosis**

### **Sphingolipidosis:**

1. GM 1 Gangliosidosis
2. GM 2 Gangliosidosis
3. Krabbe disease (KD)
4. Metachromatic LD
5. Gaucher
6. Niemann-Pick

### **Other Sphingolipidosis:**

1. Fabry
2. Farber
3. Wolman
4. Molluscoid bodies

## Gaucher Disease

### Etiology

- Glucocerebrosidase ( $\beta$ -Glucosidase) deficiency (AR<sup>1</sup>)
- **Four** mutations account for the majority of cases
- Incidence in Jews = 1/1.000
- Carrier rate in Jews = 1/18

**Gaucher should be considered in the DD of any child with unexplained organomegaly**

### Clinical Picture

	Type 1* (99%)	Type 2	Type 3
Other Names	Adult type Non-Neuropathic	Infantile Acute neuropathic	Juvenile Subacute neuropathic
Onset	Variable	Infancy	Early childhood > 2yrs
C/P	<ul style="list-style-type: none"> <li>▪ HSM (S &gt; L)</li> <li>▪ Anemia</li> <li>▪ Thrombocytopenia</li> <li>▪ Bruises</li> <li>▪ Bony pains</li> <li>▪ Pathologic fractures</li> <li>▪ Normal mentality</li> <li>(?? Chronic disease)</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ Hypertonia</li> <li>▪ Head retraction</li> <li>▪ Laryngospasm</li> <li>▪ Stridor</li> <li>▪ Squint</li> <li>▪ Cranial nerve...</li> <li>▪ Rapid <b>neurologic</b>...MR</li> <li>▪ Death in the 1<sup>st</sup> 2 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ <b>Neurologic</b> (Less severe)</li> <li>▪ MR</li> <li>▪ Ataxia</li> <li>▪ Myoclonic epilepsy</li> <li>▪ Gaze palsy</li> <li>▪ Death by age of 10-15 y</li> </ul>

### Investigations

- X-rays: Lytic lesions, Erlenmeyer flask deformity (Distal femur)
- BM examination: Gaucher cells (Positive PAS stain)
- Enzyme assay: Leukocytes or fibroblast
- Carrier detection: Molecular testing (4)
- Antenatal diagnosis is available

**Not Pathognomonic**

### Treatment

- Enzyme replacement: Cerezyme (IV infusion every other week). No effect on CNS
- BMT
- Gene therapy

# Niemann-Pick Disease

## Etiology

- Type A & B: Sphingomyelinase deficiency (AR<sup>11</sup>)
- Type C: Defective cholesterol transport (with 2ry sphingomyelinase deficiency)

## Clinical Picture

	Type A	Type B	Type C
<b>Other Names</b>	Acute infantile	Non-Neuropathic	* Neuropathic
<b>Onset</b>	1 <sup>st</sup> few months of life	Infancy or childhood	Early childhood > 2yrs
<b>C/P</b>	<ul style="list-style-type: none"> <li>▪ HSM (L &gt; S)</li> <li>▪ FTT, feeding difficulties</li> <li>▪ Neurological...MR</li> <li>▪ Cherry-red spots (50%)</li> <li>▪ Spasticity</li> <li>▪ Death in the 1<sup>st</sup> 3 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ Pulmonary involvement</li> <li>▪ Dyspnea, pneumonia</li> <li>▪ No neurological...</li> <li>▪ Normal mentality</li> <li>▪ Hypersplenism</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Slowly progressive neurologic course</li> <li>▪ Gaze palsy</li> <li>▪ HSM (<i>Less severe</i>)</li> </ul>

## Investigations

- BM examination: Foam cells (NP cells)
- Enzyme assay (Leukocytes or fibroblasts)
- CXR (Type B): Reticular or nodular infiltration
- Antenatal diagnosis is available

## Treatment

- Supportive
- Liver transplantation
- Enzyme therapy in type B (Phase I trial)

# Farber Disease

## Etiology

- Ceramidase deficiency (AR)
- Accumulation of ceramide in various tissues, especially the joints

## Clinical Picture

- Onset: 1<sup>st</sup> year of life
- Joint: Painful swelling & nodules
- Vocal cord nodules: Hoarseness of voice

## Investigations

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## Treatment

- Supportive



# Fabry Disease

(See before)

# **Gangliosidosis**

**Definition** Accumulation of gangliosides (Glycosphingolipids)

## **GM<sub>1</sub> Gangliosidosis**

### **Etiology**

-  $\beta$ -Galactosidase deficiency (AR)  $\rightarrow$  Accumulation of GM<sub>1</sub> gangliosides (CNS)

### **Clinical Picture**

	Infantile*	Juvenile	Adult
Other Names	Type 1	Type 2	Type 3
Onset	Birth	1 year	Adult
C/P	<ul style="list-style-type: none"> <li>▪ Poor feeding</li> <li>▪ HSM</li> <li>▪ Global developmental delay</li> <li>▪ Seizures</li> <li>▪ Spasticity</li> <li>▪ Hurler-like...</li> <li>▪ Dysostosis multiplex</li> <li>▪ Blindness &amp; Deafness</li> <li>▪ Cherry-red spots</li> <li>▪ Angiokeratoma</li> <li>▪ Death in the 1<sup>st</sup> 3 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Mental retardation</li> <li>▪ Seizures</li> <li>▪ Spasticity</li> <li>▪ Blindness</li> <li>▪ No HSM</li> <li>▪ No Hurler-like...</li> <li>▪ Death in the 1<sup>st</sup> 10 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Spasticity</li> <li>▪ Dysarthria</li> <li>▪ <math>\downarrow\downarrow</math> Cognitive function</li> </ul>

## **GM<sub>2</sub> Gangliosidosis**

### **Etiology**

- Tay-Sachs: AR<sup>15</sup> Sandhoffs: AR<sup>5</sup>
- Carrier rate of Tay-Sachs in Jews = 1/25

### **Clinical Picture**

	Tay-Sachs	Sandhoff	Juvenile & Adult
Genetics	HEXA gene (Chromosome 15)	HEXB gene (Chromosome 5)	-
Defect	Hexosaminidase A	Hexosaminidase A & B	-
Onset	5-6 months		Childhood-adult
C/P	<ul style="list-style-type: none"> <li>▪ Marked startle reaction (= Hyperacusis)</li> <li>▪ Regression</li> <li>▪ No HSM</li> <li>▪ Seizures</li> </ul>	<ul style="list-style-type: none"> <li>▪ Early hypotonia <math>\rightarrow</math> Spasticity</li> <li>▪ Blindness &amp; Deafness</li> <li>▪ Macrocephaly</li> <li>▪ Cherry-red spots</li> <li>▪ Death in the 1<sup>st</sup> 3-5 yrs</li> <li><b>Splenomegaly in Sandhoff</b></li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Spasticity</li> <li>▪ Dysarthria</li> </ul>

### **Investigations**

- Enzyme assay: Leukocytes or fibroblast
- Antenatal diagnosis & carrier detection is available (Enzyme activity)

**Treatment** Supportive



# **Krabbe Disease**

(Globoid Cell Leukodystrophy)

## **Etiology**

- Galactocerebroside  $\beta$ -Galactosidase deficiency (AR<sup>14</sup>)

## **Clinical Picture**

- Onset: 1<sup>st</sup> months of life
- Irritability, crying, spasticity, opisthotonos, seizures
- Neuropathy

(DD: Colic, milk allergy...)

## **Investigations**

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## **Treatment**

- Stem cell transplantation may improve the outcome if given very early

# **Metachromatic Leukodystrophy**

## **Etiology**

- Arylsulfatase deficiency (AR<sup>22</sup>)
- Accumulation of cerebroside sulfate  $\rightarrow$  Myelin destruction (*CNS & peripheral nerves*)
- Classified into: Late infantile, juvenile & adult types

## **Clinical Picture**

- Onset: 1-2 year
- Regression (Loss of ability to walk...)
- Hypotonia
- Seizures
- Neuropathy
- Juvenile MLD: Delayed onset (5 yrs) with ataxia, seizures
- Adult MLD: Onset (2<sup>nd</sup>-6<sup>th</sup> decade) with personality & psychiatric changes

## **Investigations**

- $\downarrow\downarrow$  NCV,  $\uparrow\uparrow$  CSF proteins\
- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## **Treatment**

- Stem cell transplantation may improve the outcome if given very early

# **Wolman Disease**

**Etiology** Acid lipase deficiency (AR)  $\rightarrow$  Accumulation of cholesterol esters

**Clinical Picture** FTT + Steatorrhea + HSM + Calcification of the adrenal glands

# Neuronal Ceroid Lipofuscinosis

## Definition

- Lysosomal storage disorder
- Intracellular accumulation of fluorescent lipopigments, ceroid & lipofuscin
- The number of NCL is 10
- NCL is characterized by visual loss, seizures, motor deterioration & early death
- Traditionally classified into: Infantile, Late infantile & juvenile types

## Clinical Picture

	<u>Infantile</u> <u>INCL</u>	<u>Late infantile</u> <u>LINCL</u>	<u>Juvenile</u> <u>JNCL</u>
<b>Defect</b>	Palmitoyl-protein thioesterase-1 (Chromosome 1)	Tripeptidyl peptidase-1	Membrane protein
<b>Onset</b>	1 year	2-4 years	4-10 years
<b>C/P</b>	<ul style="list-style-type: none"> <li>▪ Myoclonic seizures</li> <li>▪ Intellectual deterioration</li> <li>▪ Blindness</li> <li>▪ Ataxia</li> <li>▪ Death in childhood</li> </ul>	<ul style="list-style-type: none"> <li>▪ Myoclonic seizures</li> <li>▪ Intellectual deterioration</li> <li>▪ Blindness</li> <li>▪ Retinitis pigmentosa</li> <li>▪ Ataxia</li> </ul>	<ul style="list-style-type: none"> <li>▪ Blindness* (progressive)</li> <li>▪ Retinitis pigmentosa</li> <li>▪ Personality &amp; cognitive</li> <li>▪ Parkinsonism</li> <li>▪ Myoclonic seizures</li> </ul>

## Investigations

- ERG, VEP
- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## Treatment

- Supportive

# Menkes Disease

(Kinky hair disease)

## Etiology

- XLR disease
- Defect in copper-transporting ATPase
- Low serum copper & ceruloplasmin and ↓↓ intestinal copper absorption

## Clinical Picture

- Onset: 1<sup>st</sup> months of life
- Hypothermia, hypotonia, seizures
- Kinky colorless friable hair
- Mental retardation & optic atrophy are **constant**
- Microscopic hair examination: Trichorrhexis nodosa (*hair shaft fracture*)  
Pili torti (*twisted hair*)

## Treatment

Early SC copper-histidine (Neonatal or even fetal)

# Adrenoleukodystrophy

## Definition

- Peroxisomal disorder characterized by accumulation of VLCFA in CNS & adrenal cortex
- Neonatal ALD & XL-ALD

## XL-Adrenoleukodystrophy

### Etiology

- Defect in peroxisomal degradation of VLCFA (Due to ↓↓ **long-chain 3-oxo-CoA ligase**)
- Accumulation of VLCFA in CNS & adrenal cortex
- Locus: Xq28
- Not rare; 1:20.000 ♂

### Pathogenesis

- Accumulation of VLCFA → adrenal dysfunction
- CNS: Inflammation (Demyelination); mostly in the parieto-occipital area

### Clinical Picture "Five phenotypes are recognized"

#### A) Childhood cerebral form

- Onset: 4-8 years
- Hyperactivity (DD: ADHD), academic deterioration
- Impaired auditory discrimination, visual disturbance, ataxia
- Seizures, spastic quadriplegia
- Bulbar manifestations
- ↑↑ ICT, unilateral mass lesion
- **Adrenal insufficiency**: Usually follows but may precede neurologic manifestations

#### B) Adolescent ALD: Delayed onset & less progressive course

#### C) Adrenomyeloneuropathy

- Affection of spinal cord & peripheral nerves in adolescents & adults
- Progressive paraparesis, urinary incontinence, impotence

#### D) Addison only: 25% of Addison patients have biochemical defects of ALD, so...

#### E) Asymptomatic ALD

NB: 50% of heterozygous ♀ may have milder adrenomyeloneuropathy

### Investigations

- ↑↑ VLCFA in plasma, RBC, fibroblasts
- CT, MRI: Typically symmetric periventricular in the posterior parietal & occipital lobes  
Unilateral lesion with mass effect (DD: Tumor) may occur
- Adrenal function tests: ACTH, cortisol after ACTH stimulation

### Treatment

- **BMT**: Considered in neurologically asymptomatic or mildly affected patients
- **Lorenzo's oil**: ↓↓ VLCFA synthesis
- Adrenal replacement

### Prevention & Genetic counseling

- **Family screening**: VLCFA (allows early diagnosis of presymptomatic individuals, why?)
- **Antenatal diagnosis**: VLCFA (amniocytes or CVS) or molecular testing
- Addison males

**DD** ADHD, other leukodystrophies, MS, brain tumors, epilepsy, Addison



## Neonatal Adrenoleukodystrophy

- Defective peroxisome biogenesis (Peroxisome import)
- AR
- Marked hypotonia
- Seizures
- Severe developmental delay
- Optic atrophy (visual affection)
- Deafness
- Adrenal function is usually impaired

## Alexander Disease

Etiology AD<sup>17</sup>

### Clinical Picture

- Onset: 1<sup>st</sup> months of life
- Regression, seizures, spasticity
- Death by 5 yrs

## Canavan Disease

### Etiology

- AR disease
- Deficiency of aspartoacylase enzyme (↑↑ N-acetylaspartic acid in CNS, blood & urine)
- More prevalent in Jews

Pathology Spongy degeneration of the white matter

### Clinical Picture

- Onset: 1<sup>st</sup> months of life
- **Macrocephaly**, severe hypotonia followed by hypertonia & spasticity
- Joint stiffness & contractures
- Seizures
- Feeding difficulties, aspiration

### Investigations

- ↑↑ Urinary & CSF N-acetylaspartic acid
- **Enzyme assay**: aspartoacylase enzyme
- **MRI**: White matter degeneration in the cerebral hemispheres
- **MRS**: High peak of N-acetylaspartic acid

Treatment (No specific Rx)

- Trials of aspartoacylase (delivery across BBB)

## Rett Syndrome

Clinical Picture (predominantly in ♀)

- Onset: 1<sup>st</sup> year of life
- Regression, abnormal respiration (Sighing & apnea), seizures
- **Repetitive hand wringing movements**: at 2-3 yr of age

DD: CP

# Floppy Infant

## Definition

Infant with severe persistent hypotonia

## Etiology

### A) Central Hypotonia

1. Chromosomal
  - Trisomies: Down syndrome
  - Prader-Willi syndrome
2. Peroxisomal
  - Zellweger \$ (Cerebrohepato renal)
  - Neonatal adrenoleukodystrophy
3. Atonic CP
4. Kernicterus
5. HIE
6. ICH
7. Familial dysautonomia
8. Oculocerebrorenal syndrome (Lowe syndrome)
9. Gangliosidosis
10. Leukodystrophy
  - Menkes disease (Kinky hair disease)
  - Neonatal adrenoleukodystrophy

### Atonic CP

Hypotonia & brisk reflexes

### B) N/M causes (Motor unit disorders)

1. Spinal cord disorders
2. AHC disease: Werdnig-Hoffmann syndrome (SMA type1)
3. Polyneuropathy
  - HMSN Type 3 (Dejerine Sottas Disease)
  - Giant Axonal Neuropathy
  - Congenital Hypomyelinating Neuropathy
4. N/M junction disorders
  - Congenital (Familial) myasthenia: (↓↓ or absent ACh receptors)
  - Transient neonatal myasthenia: Transplacental passage of Ab (Myasthenic mother)
  - Infant Botulism
5. Myopathy
  - Benign congenital hypotonia
  - Congenital myopathy (Myotubular, Nemaline-rod, CMFTD)
  - Metabolic: GSD type 2 (Pompe), mitochondrial myopathy
  - Muscular Dystrophy: Congenital muscular dystrophy, Myotonic dystrophy

## Clinical Picture

### ☒ Diagnosis of floppy infant (Hypotonia)

- Head lag, ventral suspension & frog-leg position

### ☒ Clues to the diagnosis of cerebral hypotonia

- Disturbed consciousness
- Dysmorphic facies
- Seizures
- Normal or brisk reflexes

### ☒ Clues to the diagnosis of Motor unit disorders

- Fasciculations
- Hyporeflexia

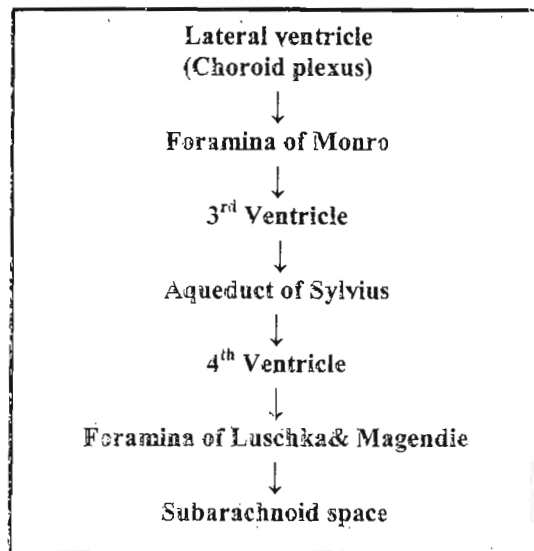
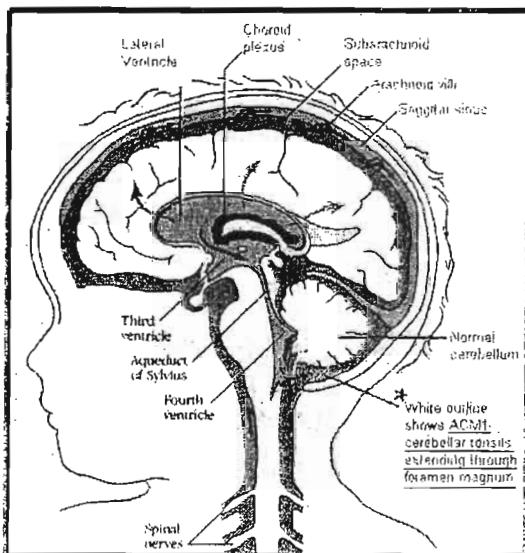
## Investigations & Treatment

# Hydrocephalus

## CSF Circulation

- A) **Secretion:** Choroid plexus (mainly in the lateral ventricles)  
 B) **Circulation:** See below  
 C) **Absorption:** Subarachnoid space (Arachnoid villi)

**CSF volume:**  
 Infants = 50 cc  
 Adults = 150 cc



## Definition

Dilatation of the ventricular system due to  $\uparrow\uparrow$  CSF volume with or without  $\uparrow\uparrow$  CSF pressure

## Classification

### A) Communicating Hydrocephalus

- a.  $\uparrow\uparrow$  **Formation:** Choroid plexus papilloma (Lateral ventricle\*)  
 b.  $\downarrow\downarrow$  **Absorption:**
- Subarachnoid hemorrhage
  - Post-meningitis (bacterial & TB)
  - Leukemia
  - MPS & achondroplasia
  - SSS thrombosis
  - Arnold-Chiari malformation (Type II):
    - Downward displacement of the cerebellar vermis, pons & medulla into the cervical canal  $\rightarrow$  Obstruction of the subarachnoid space
    - Usually associated with myelomeningocele
    - Stridor, weak cry & apnea (10% of patients)

### B) Obstructive Hydrocephalus

#### a. Congenital

- Stenosis of the aqueduct of Sylvius (infectious or XLR)
- AD, AR
- Aneurysm of vein of Galen  $\rightarrow$
- Tuberous sclerosis & NF
- Dandy-Walker malformation
  - Abnormal development of the roof of the 4<sup>th</sup> ventricle (# Magendie & Luschka)
  - Cystic expansion of the 4<sup>th</sup> ventricle
  - Cerebellar hypoplasia (Ataxia)

**Cranial Bruit**

- b. **Acquired:** Post-meningitis (bacterial & TB), Post-hemorrhagic, tumors or abscess

	Obstructive	Communicating
<b>Congenital</b>	<ul style="list-style-type: none"> <li>• Aqueductal stenosis</li> <li>• Dandy-Walker malformation</li> <li>• Malformation of vein of Galen</li> <li>• Tuberous sclerosis &amp; NF</li> </ul>	<ul style="list-style-type: none"> <li>• Arnold-Chiari malformation</li> <li>• Achondroplasia</li> <li>• MPS</li> </ul>
<b>Traumatic</b>	Intraventricular Hge	Subarachnoid Hge
<b>Inflammatory</b>	Post-meningitic gliosis	Post-meningitic gliosis
<b>Neoplastic</b>	Posterior fossa tumor	Leukemia (Metastatic deposits)
<b>Others</b>	Brain abscess	↑↑ CSF formation (Choroid plexus papilloma)

## Clinical Picture

### A) In infancy (Before suture closure)

#### a. General examination

- ☒ Macrocephaly & Progressive ↑↑ in head size
- ☒ Bulging AF & separated sutures
- ☒ Stretched scalp skin & dilated scalp veins
- ☒ Sun set sign (Downward displacement of the eyes)
- ☒ Skull percussion: Macewen sign (Cracked pot sign)
- ☒ Meningomyelocele: in Chiari malformation
- ☒ Manifestations of ↑↑ ICP (Vomiting, headache, blurring of vision): Not prominent



#### b. Neurological manifestations examination

- ☒ Delayed developmental milestones (Motor & Mental)
- ☒ Neurological examination
  - Tone: Hypertonia (Spasticity)
  - Power: Weakness or paralysis
  - Deep reflexes: Hyperreflexia (± Pathological reflexes ± Clonus)
  - Cranial nerves: Optic nerve atrophy (in chronic untreated patients)

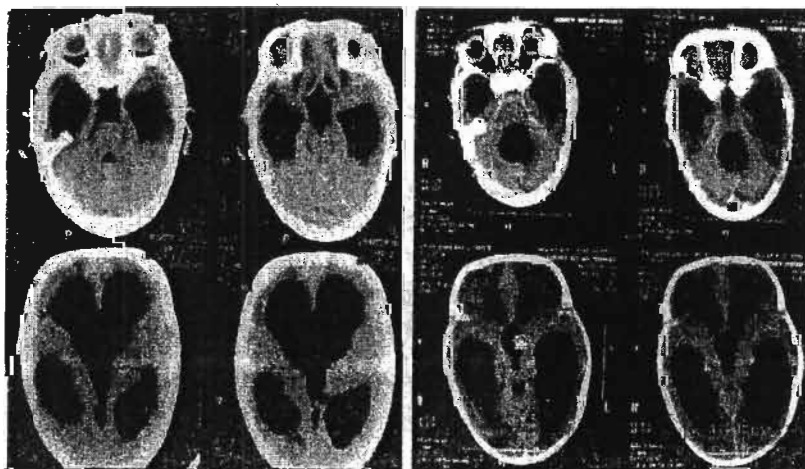
Hypotonia with meningomyelocele.

### B) In older children (After partial suture closure)

- ☒ Head enlargement is less evident (Closed suture)
- ☒ Manifestation of ↑↑ ICP are prominent (Headache, vomiting & blurring of vision)
- ☒ Neurological & ocular: as before

## Investigations

- Skull X-ray: Craniofacial disproportion & separation of the sutures  
Silver beaten appearance (in older children)
- Cranial US, CT, MRI brain
- Investigations of the cause



## Treatment

### A) Medical Treatment

Acetazolamide (10-15 mg/Kg/day): ↓↓ CSF production

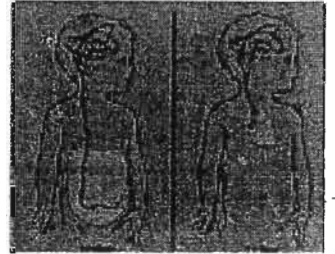
### B) Surgical Treatment (= Shunt)

#### Types

- Ventriculoperitoneal shunt
- Ventriculoatrial shunt
- Endoscopic 3<sup>rd</sup> ventriculostomy (ETV)
- External ventricular drainage

#### Complications

- Infection\* (Staphylococcus epidermidis\*)
- Obstruction (2<sup>nd</sup> try to infection)
- Shunt nephritis



## Prognosis

- Visual: Vision loss & field defects
- Intellectual: ↓↓ IQ
- Precocious puberty: ↑↑ GnRH
- Complications of Rx

## Differential Diagnosis

Causes of Macrocephaly

## Macrocephaly

### Definition

Skull circumference > 95<sup>th</sup> % for age, sex & race

### Etiology

1. Hydrocephalus
2. Cranial (Skeletal)
  - Chronic hemolytic anemia
  - Rickets
  - Achondroplasia (large head, short limbs & normal trunk) + Normal mentality
  - MPS
  - Familial large head
3. Megalencephaly (Abnormal storage of substances within the brain parenchyma)
  - ~~Benign~~ familial megalencephaly
  - Leukodystrophy: Canavan & Alexander
  - Gray matter diseases: GM1, GM2
4. Chronic subdural collections
5. Brain tumors
6. Hydranencephaly
  - Congenital absence of cerebral hemispheres (Cranium is filled with CSF)
  - Relatively intact brain stem
  - +Ve Transillumination
  - Poor feeding, seizures, quadriplegia, MR
  - Cause: Bilateral occlusion of ICAs
  - Rx: Shunt

# Microcephaly

## Definition

Skull circumference < 5<sup>th</sup> % for age, sex & race

## Etiology

### A) Primary

1. **Familial microcephaly** (AR or AD): MR, seizures, camel-shaped head

### 2. Syndromes

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)
- Cri-du-chat syndrome (5p-)
- Cornelia De Lange (Microcephaly, short stature, synophrys...)
- Smith-Lemli-Opitz (Microcephaly, ptosis, ambiguous genitalia)

### B) Secondary (Injury of the developing brain) ? causes



**Synophrys** = Eyebrows that meet in the midline

# Craniosynostosis

## Definition

Premature closure of one or more cranial sutures

## Classifications

### A) Primary (Abnormal skull development)

### B) Secondary (Injury of the developing brain)

## Clinical Picture

### 1. Abnormal skull shape

- **Dolicocephaly** (Long narrow skull)
- **Brachycephaly** (↓↓ AP diameter)
- **Frontal Plagiocephaly** (Unilateral flattening of the forehead)
- **Occipital Plagiocephaly** (Unilateral flattening of the occiput)
- **Oxycephaly** (Acrocephaly or Turriccephaly): High head
- **Trigonocephaly** (Keel-shaped forehead & hypotelorism)
- **Kleeblattschadel** skull (Clover leaf-shaped skull)

### 2. Palpation of the sutures: Fusion of bones with bony ridge

### 3. ↑↑ ICP & hydrocephalus

## Investigations

- Skull X-ray: Fusion of the sutures ± Silver beaten appearance
- CT brain

## Treatment Craniectomy (Suture separation)

## Genetic syndromes

Genetic syndromes			
<b>Crouzon</b>	AD	Coronal sutures Brachycephaly	Proptosis Hypertelorism
<b>Apert</b>	Sporadic	Multiple sutures Acrocephaly	Syndactyly of all fingers
<b>Carpenter</b>	AR	Kleeblattschadel	MR. Polydactyly & Syndactyly
<b>Chotzen</b>	AD	Plagiocephaly	Ptosis, Syndactyly
<b>Pfeiffer</b>	Sporadic	Acrocephaly	Short broad thumbs & toes



# Cerebral Palsy

(Little Disease)

Not Static encephalopathy

## Definition

Non-fatal, Non-curable group of **motor** syndromes resulting from disorders of early brain development

## Incidence

2-4/1000 live births

Prematurity is a risk factor

75% of cases are idiopathic

## Etiology

- ☒ **Prenatal:** Congenital infection, Congenital anomalies, Radiation, Toxins (Alcohol, cocaine)
- ☒ **Natal:** HIE, birth injury (ICH)
- ☒ **Postnatal:** CNS infection (meningitis), trauma, ICH, ↓↓ G, ↓↓ Na, ↑↑ Na, kernicterus

## Classification

### A) Topographic

- Monoplegic
- Paraplegic
- Hemiplegic
- Triplegic
- Quadriplegic
  - Diplegic: (Spasticity is more in LL)
  - Double hemiplegic (Spasticity is more in UL)

### B) Clinical type

- Spastic
- Atonic
- Extrapyrarnidal (ataxic, dystonia & Choreoathetosis)
- Mixed

### C) Functional Classification

- Class 1: No limitation of activity
- Class 2: Mild
- Class 3: Moderate
- Class 4: Severe

### D) Associated deficits (MOTOR)

- MR
- Epilepsy
- Microcephaly
- Hearing, visual & speech abnormalities
- Behavioral & emotional disturbances
- Persistent primitive reflexes (Moro reflex)

## Clinical Picture

Frequency	Most common	Less common	Less common
Etiology	Damage of $\Delta$ tract		Kernicterus (BG)
Power	Weakness or paralysis	Weakness or paralysis	Weakness
Tone	Hypertonia	Hypotonia	Hypotonia then hypertonia
Reflexes	Hyperreflexia	Brisk reflexes	No hyperreflexia
Others	Pseudobulbar-Scissoring	MR is usually marked	Deafness is usual

## Investigations

- CT brain: Brain atrophy
- Investigation of the cause (e.g., TORCH...)

CP is a diagnosis of exclusion

## Treatment (Supportive-Team of physicians)

### A) Care of the parents

### B) Care of the child

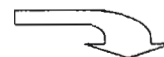
- Physiotherapy
- Nutritional
- Rx of seizures
- Rehabilitation & occupational support
- Spasticity & contractures: Baclofen, botulinum toxin
- Dystonia: trihexyphenidyl

# Mental Retardation

## Definition

Delayed mental developmental milestones, manifested as:

- a. **Infancy:** Delayed social development
- b. **Early childhood:** Delayed speech
- c. **Late childhood:** Learning difficulties & school underachievement



## Etiology

### A) Non-organic MR (90%)

- Usually mild
- Low socioeconomic class
- ??Nutritional, infection, illiteracy

- Social smile
- Recognition of the mother
- Laugh
- Mama & Dada
- Waving bye-bye

### B) Organic MR

#### a. Genetic

##### 1. Chromosomal

- Trisomies: Down syndrome
- Prader-Willi syndrome
- Fragile X syndrome

##### 2. Neurocutaneous syndromes

- Tuberous sclerosis (60-70%)
- Neurofibromatosis (10%)

##### 3. Degenerative brain diseases

- Degeneration of the gray matter
- Degeneration of the white matter

##### 4. Inborn errors of metabolism

- Aminoacids: PKU, Tyrosinemia, Homocystinuria, Maple syrup urine disease
- Lipid storage diseases: Gaucher (Type 2 & 3) & Niemann-Pick (Type A & C)
- CHO: Galactosemia, MPS (Types??)
- Organic acidemia: Propionic acidemia
- Mitochondrial: MELAS, MERRF, KSS, Leigh disease

##### 5. Congenital brain anomalies

- Agenesis of the corpus callosum
- Neuronal migration disorders (Lissencephaly, Schizencephaly, Porencephaly)
- Microcephaly & Craniosynostosis

**Fragile X** is the 2<sup>nd</sup> most common genetic cause of MR after Down S

#### b. Non-genetic

- ☒ **Prenatal:** Congenital infection, Congenital anomalies, Radiation, Toxins
- ☒ **Natal:** HIE, birth injury (ICH)
- ☒ **Postnatal:** CNS infection (meningitis), trauma, ICH, ↓↓ G, ↓↓ Na, ↑↑ Na, kernicterus
- ☒ **Hypothyroidism**

## Degree of MR

**Intelligence Quotient (IQ)** = Mental age/Chronological age %

Several tests are available e.g., Stanford-Binet test

<b>Mild</b>	50-70	Late childhood	Learning	<b>Educable-Special classes</b>
<b>Moderate</b>	35-50	Early childhood	Speech	<b>Trainable-Special classes</b>
<b>Severe</b>	20-35	Infancy	Social	Minimal self-care
<b>Profound</b>	< 20	Infancy	Social	Total supervision



## Clinical Picture

- Delayed mental milestones
- Delayed motor milestones is usually present
- C/P of the cause [Down, organomegaly, macro-orchidism, cherry-red spots...]




## Investigations

### A) laboratory:

- Reducing substances in urine
- Urine succinylacetone
- Karyotyping
- TORCH
- Serum & urine aminogram
- T<sub>3</sub> & T<sub>4</sub>

### B) Imaging:

- Skull X-ray 
- CT & MRI
- US & Echo-

### Cherry-red spots

- GM1
- GM2
  - Tay-Sachs
  - Sandhoff
- Niemann-Pick
- Metachromatic LD
- Sialidosis

### Intracranial Calcification

- Neurocutaneous \$
  - Tuberous sclerosis
  - Sturge-Weber
- Congenital infections
  - CMV: periventricular
  - Toxoplasmosis: Diffuse
- Tumors: Craniopharyngioma
- Metabolic: Hypoparathyroidism
- Infection: meningitis & abscess

## Prevention

- ☒ Proper antenatal care (High-risk pregnancies)
- ☒ Proper intrapartum management (Hypoxia, birth injury)
- ☒ Proper postpartum management (NJ, metabolic causes)
- ☒ Antenatal diagnosis ± (?Therapeutic abortion)
- ☒ Early diagnosis of treatable conditions: Hypothyroidism, galactosemia, PKU. How??
- ☒ Proper Rx of situations associated with risk of development of acquired MR
  - Proper neonatal resuscitation
  - Prolonged convulsions
  - Meningitis
  - Coma (encephalopathy)

## Treatment (Supportive)

### A) Care of the parents

- Telling bad news
- Genetic counseling (RR in Down, AR conditions...)
- Continuous support

### B) Care of the child

- Drug therapy: Piracetam (*Nootropil* or *Stimulan*) & other drugs are of doubtful value
- Continuous supervision: Poisoning, trauma, accidents
- Education & training according to the degree of MR (specialized centers, schools)

# Encephalopathy

(Coma)

## Definition

It is diffuse brain disorder characterized by 2 of the following:

1. Altered state of consciousness (DCL)
2. Altered cognition or personality
3. Seizures

**Encephalitis** = Encephalopathy + CSF pleocytosis

**Consciousness** = Self-awareness (It is dependent on RAS & cerebral cortex)

**Coma** = State of prolonged unconsciousness in which the patient can not be aroused even by painful stimuli (rubbing of sternum, pressure on fingernails). It results from:

1. Bilateral diffuse cortical lesion
2. Small focal brain stem lesion

## Level of Consciousness

### A) Staging System (more simple)

- a. Fully consciousness
- b. Lethargy (Sleepy)
- c. Confusion (Disoriented)
- d. Coma

1. Stupor (can be aroused for < 1 min.)
2. Light coma: responds to painful stimuli by:
  - a. Flexion withdrawal or;
  - b. Decorticate extension (flexion of UL & extension of LL) or;
  - c. Decerebrate extension (extension of the 4 limbs)
3. Deep coma (No response but with spontaneous breathing)
4. Deep coma with apnea (if not ventilated, brain death occurs in 4 minutes)

### Brain Death

1. Deep coma with apnea
2. Lost brainstem reflexes
3. No hypotension, hypothermia or CNS depressants drugs
4. Persistent findings throughout period of observation (12-24 hrs)
5. EEG is needed only in infants < 1 yr

### B) Scoring System (more accurate)

#### Glasgow coma scale

Spontaneous	4	Oriented & appropriate	5	Spontaneous	6
To voice/ touch	3	Words/ irritable cry	4	Flexion withdrawal to touch	5
To pain	2	Cries to pain	3	Flexion withdrawal to pain	4
No response	1	Moans to pain	2	Decorticate extension	3
		No response	1	Decerebrate extension	2
				No response	1

Total score = 15    Minimal score = 3    Score < 8 indicates severe neurological injury

#### Morray coma scale (Used in ventilated & mechanically ventilated)

Spontaneous	6	All normal	4
Flexion withdrawal to touch	5	Some absent	3
Flexion withdrawal to pain	4	All absent but breathing	2
Decorticate extension	3	All absent & apneic	1
Decerebrate extension	2		
No response	1		

#### Brain stem reflexes:

1. Light reflex
2. Corneal reflex
3. Oculocephalic
4. Oculovestibular
5. Cough / gag reflex

**Etiology** (= Causes of coma & Lethargy)**1. CNS infection**

- Meningitis
- Encephalitis
- Brain abscess
- Severe septicemia
- Acute disseminating encephalomyelitis (ADEM) = Postinfectious encephalomyelitis
- Post immunization encephalopathy

**2. ICH (Intracerebral, Epidural, Subdural...)**

- Traumatic
- Non traumatic
  - ☒ Bleeding tendency...
  - ☒ Ruptured aneurysm
  - ☒ AV malformation
  - ☒ Hypertension

**3. Infarction**

- Thrombosis (congenital / acquired)
- Embolism (cardiac)

**4. Brain tumors**

- Infratentorial
- Supratentorial

**5. Epilepsy\***

- Status epilepticus
- Post-ictal state

**6. Trauma**

- Concussion
- Contusion

**7. Migraine\*****8. ↑↑ ICT (all causes)**

- ↑↑ brain volume (brain edema)
- ↑↑ Blood flow (hyperthermia, HTN, convulsions, ↓↓ O<sub>2</sub>, ↑↑ CO<sub>2</sub>)
- ↑↑ CSF (hydrocephalus)
- Pathologic masses

**ADEM**

- **Def:** Inflammation of brain & spinal cord
- **Path:** Damage of myeline
- **Etiology:** Postinfectious or postvaccination
- **C/P:** Headache, lethargy, coma, seizures, paralysis, sensory loss...
- **Investigations:** MRI, CSF
- **Rx:** IVIG, steroid (methylprednisolone)

**1. Hypoxic Encephalopathy**

- Hypoxic-hypoxic encephalopathy
  - ☒ Airway obstruction
  - ☒ Respiratory failure
  - ☒ Post-CPR
- Hypoxic-ischemic encephalopathy
  - ☒ Advanced shock
- Hypoxic-anemic encephalopathy
  - ☒ Severe hemorrhage
  - ☒ Severe hemolysis

**2. Exogenous Encephalopathy (Poisoning)**

- Narcotics (Miosis, ↓↓ RC)
- Salicylates (acidosis, hyperventilation)
- Organophosphorus (PPP)
- Alcohol
- Lead poisoning

**3. Endogenous Encephalopathy**

- Organ failure
  - ☒ ARF
  - ☒ CRF (Uremia)
  - ☒ Dialysis dysequilibrium
  - ☒ Acute hepatic failure
  - ☒ Reye syndrome
- Electrolyte disturbances
  - ☒ ↓↓ Na, ↑↑ Na
  - ☒ ↓↓ Ca, ↓↓ Mg
- Endocrinal
  - ☒ DKA
  - ☒ Hypoglycemia\*
  - ☒ Thyrotoxic crisis
- HTN encephalopathy (edema & Hge)
- Inborn errors of metabolism\*
  - ☒ GSD (hypoglycemia)
  - ☒ Urea cycle defects (↑↑ NH<sub>3</sub>)
  - ☒ Zellweger \$ (Cerebrohepatorenal)
  - ☒ FA oxidation defects: MCAD deficiency (hypoglycemia)
  - ☒ Mitochondrial encephalopathy (MERRF, MELAS, KSS, Leigh, ...)
  - ☒ Disorders of pyruvate metabolism
- Radiation: BV injury → edema & Hge
- Burn\*
- TPN (↑↑ NH<sub>3</sub>)
- Thiamine (B<sub>1</sub>) deficiency

(Recurrent encephalopathy = \*)

## History Taking

Fever, trauma, DM, oliguria, edema, drugs, toxins, family history

## Examination

### A) Level of Dysfunction

<b>Cortex</b>	Flexion withdrawal	Small reactive	Normal or Cheyne-Stokes
<b>Thalamus</b>	Decorticate	Small reactive	Normal or Cheyne-Stokes
<b>Midbrain</b>	Decerebrate	Midposition	Neurogenic hypoventilation
<b>Pons</b>	No response	PPP	Normal or apneustic
<b>Medulla</b>	No response	Small reactive	Irregular (ataxic)

### B) Lateralizing signs

- ☒ Asymmetric motor response
- ☒ Asymmetric brain stem reflexes
- ☒ Uncal herniation (Unilateral dilated irreactive pupil)
- ☒ Focal neurological deficit (focal seizures)

Response	Symmetric	Asymmetric
Causes	Encephalopathy	Abscess, tumor, Hge, infarction

### C) Physical signs

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Airway obstruction | <input checked="" type="checkbox"/> Head trauma               |
| <input checked="" type="checkbox"/> RD                 | <input checked="" type="checkbox"/> Chest or Abdominal trauma |
| <input checked="" type="checkbox"/> Hypoventilation    | <input checked="" type="checkbox"/> Organomegaly              |
| <input checked="" type="checkbox"/> Shock              | <input checked="" type="checkbox"/> Jaundice                  |
| <input checked="" type="checkbox"/> Pallor             | <input checked="" type="checkbox"/> Edema (Puffiness)         |
| <input checked="" type="checkbox"/> HTN                | <input checked="" type="checkbox"/> Purpuric eruption         |
| <input checked="" type="checkbox"/> Fever              | <input checked="" type="checkbox"/> Meningeal irritation      |
| <input checked="" type="checkbox"/> Dehydration        | <input checked="" type="checkbox"/> Lateralizing & eye signs  |

### D) Eye signs

- Dehydration, edema, jaundice, Hge, PPP, small (narcotics)
- Level of dysfunction
- Glasgow coma scale
- Diagnosis of brain death

## Management of Comatose Child

### Investigations

#### A) Early Investigations

- ABG
- Electrolytes
- Blood glucose
- Renal functions

#### B) Other Investigations

- |   |                        |
|---|------------------------|
| • Sepsis screen                             | • CT Brain             |
| • CSF examination                           | • CXR                  |
| • Liver enzymes & liver function tests      | • Abdominal X-ray & US |
| • Coagulation study                         | • Metabolic screen     |
| • Blood film for Malaria (Cerebral malaria) | • Toxic screen         |

## Treatment

### A) Nonspecific Support

#### 1. Airway

- Check patency of airway (Slight neck extension + oropharyngeal airway)
- Removal of FB & suction

#### 2. Breathing

- Oxygen therapy is mandatory in any comatose patient
- Mechanical ventilation may be required, why?

#### 3. Circulation

- Establish a vascular access
- Correction of shock, hypoglycemia & maintenance of BP

#### 4. Convulsions

- Diazepam 0.3-0.5 mg/Kg/dose
- Phenobarbitone 15-20 mg/Kg/dose
- Phenytoin 15-20 mg/Kg/dose
- Maintenance IV anticonvulsants

#### 5. ↑↑ ICP

#### 6. Respiration

- Physiotherapy & suction
- Respiratory support...

#### 7. GIT

- Prevention of stress ulcers (*Aluminum hydroxide, ranitidine, omeprazole*)
- Prevention of constipation & fecal impaction (*Lactulose, enema*)

#### 8. Eye & Skin

- Antibiotic eye drops & coverings
- Frequent change of position (# Bed sores)
- Urine bag

#### 9. Infection

- Antiseptic precautions & infection control guidelines
- Prophylactic antibiotics
- Early diagnosis & Rx of infection (sepsis screen)

#### 10. Nutrition

- NGT feeding
- TPN

#### Type of IV fluids:

- **Shock:** Ringer's Lactate or NS
- **Deficit therapy:** Glucose : NS (1:1)
- **DKA:** NS
- **Suprarenal:** G 5-10%: NS (1:1)
- **Maintenance:** Glucose : NS (4:1)
- **Avoid K** till exclusion of renal failure

### B) Specific Management

#### 1. CNS infection

- ☒ **Bacterial infection:** Ampicillin (200 mg/Kg/day) + 3<sup>rd</sup> generation cephalosporins
- ☒ **Viral infection:** Acyclovir
- ☒ **Brain abscess:** Antibiotic Rx + Neurosurgical consultation (aspiration)

#### 2. ICH: Neurosurgical consultation (?intervention)

#### 3. Hypoxic Encephalopathy

- ☒ **Hypoxia:** Respiratory support
- ☒ **Shock:** Shock therapy + inotropes
- ☒ **Anemia:** Packed RBCs

#### 4. Endogenous Encephalopathy: ARF, CRF, Suprarenal failure, Liver cell failure...

#### 5. Exogenous Encephalopathy: Organophosphorus...

# Seizures in Childhood

## Definitions

☒ **Seizure:** Transient occurrence of symptoms&/or signs due to abnormal brain electrical activity manifested as motor activity, sensory disturbance, disturbed consciousness, autonomic, psychic or mixed manifestations

☒ **Convulsions:** Involuntary muscular contraction due to abnormal electrical activity

☒ **Acute symptomatic seizures:** Seizures 2ry to acute brain insult (e.g., meningitis...)

☒ **Unprovoked seizures:** Not symptomatic seizures

☒ **Epilepsy:**  $\geq 2$  **unprovoked** seizures occurring at interval  $\geq 24$  hrs

NB: Most seizures are provoked [Fever, trauma, hypoxia, infection, toxins & arrhythmias]

☒ **Epileptic syndrome:** If there is a specific seizure type, specific age & specific prognosis

☒ **Idiopathic epilepsy:** No underlying brain disorder (usually genetic e.g., absence)

☒ **Symptomatic epilepsy:** There is underlying brain disorder (e.g., tuberous sclerosis...)

☒ **Cryptogenic epilepsy:** Epilepsy with presumed but unknown underlying brain disorder

☒ **Epileptic encephalopathy:** Epileptic syndrome with severe EEG & cognitive impairment

## Type of Motor Seizures

- Tonic:  $\uparrow\uparrow$  Muscle tone or rigidity
- Clonic: Rhythmic muscle contraction & relaxation
- Tonic-clonic
- Myoclonic: Shock-like contraction of a muscle or a group of muscles with loss of M. tone
- Atonic seizures: Lack of movement or flaccidity
- Astatic seizures: Sudden loss of muscle tone (*shorter than atonic seizures*)

## Distribution of Convulsions

- Focal (partial): Initial activation of a part of one cerebral hemisphere (Clinical & EEG)
- Generalized: Involvement of both cerebral hemispheres (Clinical & EEG)

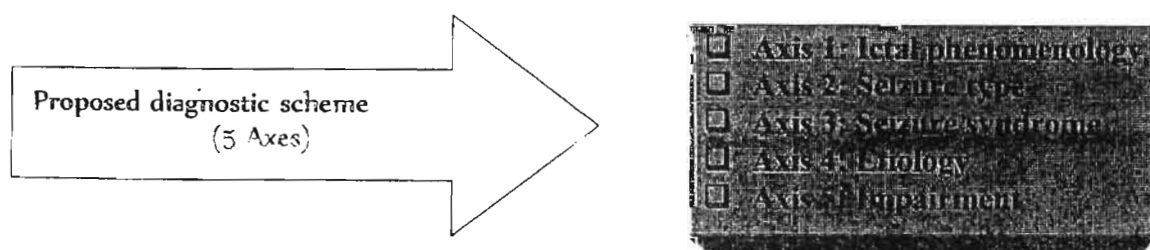
## Clinical Grading of Convulsions (Grades I-IV)

- **Short convulsive fit:** Convulsive fit lasting for few minutes
- **Prolonged convulsive fit:** Convulsive fit lasting for 15-30 minutes
- **Status epilepticus:** Convulsive fit lasting for  $> 30$  minutes OR short repetitive fits without regaining consciousness in between
- **Refractory Status epilepticus:** Status epilepticus not responding to 1<sup>st</sup> line Rx

## Mechanism of Seizures

- a. **Underlying etiology:** Stroke, tumors, channelopathies (Na, K, Ca, Cl), mutations affection Ach or GABA receptors or unknown cause
- b. **Epileptogenesis:** Brain is turned epileptic (Activation of glutamate & Ca channels)
- c.  $\uparrow\uparrow$  **Excitability**
- d. **Neuronal injury:** Swelling followed by atrophy of the hippocampus

## Evaluation of the 1<sup>st</sup> seizure



## Clinical Evaluation

### A) Stabilization

- A, B, C

### B) Diagnosis of life-threatening conditions

- CNS infections, ICH, sepsis, trauma, poisoning

### C) History

#### a. Personal history

- Febrile convulsions: 6 months-5 yrs

#### b. Present history

- Acute or recurrent seizures
- Seizure description:
  - Precipitation factors: Fever, trauma, TV, drugs (antihistamines...)
  - Aura: Epigastric pain, tingling, visual, auditory, olfactory, experiential (*Déjà vu*)
  - Onset: Focal or generalized
  - Duration, consciousness, pattern & frequency
  - Post-ictal period

- Manifestations of CNS infections

- Intellectual deterioration: Neurodegenerative diseases

- Treatment history: Type of anticonvulsants, compliance, response

#### c. Family history: Febrile convulsions or familial epilepsy syndromes

#### d. Vaccination history: Post-immunization (DPT)

#### e. Perinatal history: Antenatal, natal & postnatal

### D) Examination

#### a. Vital signs

- Temperature: Febrile convulsions...
- BP: Hypertensive encephalopathy

#### b. Anthropometric Measurements

- Skull circumference: *Microcephaly*

#### c. Head & Neck

- Eye examination: Papilledema, retinal hemorrhage, phakomas (↑↑ ICT), coloboma
- Manifestations of meningeal irritation

#### d. Skin

- Café-au-lait patches: Neurofibromatosis
- Hypopigmented macules: Tuberous sclerosis
- Port wine staining: Sturge-Weber

#### e. Abdominal examination: Organomegaly in neurometabolic causes

#### f. Neurological examination:

- Motor, Sensory, cranial nerves, meningeal irritation, IQ
- Localizing signs: Hemiparesis, plantar reflex, eye...

#### Remember

##### Causes of fever & convulsions:

- Febrile Convulsions
- CNS infection
- Toxic convulsions (Shigella, Salmonella)
- Seizures precipitated by fever

### E) Investigations

#### a. Neuro-imaging: CT or MRI

#### b. CSF: If CNS infection is suspected

#### c. Metabolic work-up

- Amino acids, organic acids, biotinidase
- Lactate, pyruvate, carnitine profile, muscle biopsy

##### Value of CSF examination:

- CNS infection
- Pyridoxine dependency
- Glucose transporter deficiency
- Cerebral folate deficiency

## Etiology of Convulsions

1. Febrile Convulsions
2. 1<sup>st</sup> Epileptic fit
3. Causes of...
4. CNS Infection, Hge, infarction
5. Trauma, tumors, ↑↑ ICT
6. Hypoxic, exogenous, endogenous...

### Causes of convulsions in GE

- ↓↓ Na, ↑↑ Na, ↓↓ Ca
- Febrile Convulsions
- Toxic convulsions
- ICH (DIC)

### 1. Idiopathic\* (80%)

- Genetic
  - ☒ AD febrile convulsions
  - ☒ Absence seizures
  - ☒ Benign familial neonatal seizures
  - ☒ Benign infantile convulsions

### • Non-genetic

### 2. Organic (Symptomatic)

- Cerebral malformation (lissencephaly...)
- Perinatal brain insult  
(hypoxia, Hge, trauma, infection, ↓↓ G)
- Neurocutaneous syndromes
- Neurodegenerative brain diseases
- Neurometabolic (urea cycle...)
- Uremia

## Febrile Convulsions

### Etiology

AD inheritance is demonstrated in some families (19p, 8q, 2q, 5q, 6q)

### Incidence

Affecting 2-5% of neurologically healthy children

Febrile convulsions are the **most common** seizure disorder of childhood

### Clinical Picture (= 5 essential criteria)

- A) Susceptible age (*Age dependent*): 6 months-5 yrs
- B) Fever: usually > 39°C (convulsions occur at the onset of rapid rise of temperature)
- C) No clinical manifestations of CNS infection: Meningeal irritation, DCL, ↑↑ ICT
- D) Clinical manifestations of extracranial infection: OM, roseola infantum, GE, pharyngitis
- E) Convulsions

	Simple febrile convulsions	Complex (Atypical)
Type	Generalized tonic-clonic	Focal
Duration	< 15 minutes	Prolonged (e.g., Febrile status epilepticus)
Frequency	Only one fit during 24 hr	More frequent
Post-ictal stupor	Short	Prolonged



## Risk of recurrence of febrile seizures

- After the 1<sup>st</sup> attack: 30% will show recurrence
- After the 2<sup>nd</sup> attack: 50% will show recurrence
- Infants < 1 year: 50% will show recurrence
- Factors that the ↑↑ risk of recurrence: ♂ sex, family history of febrile seizures or epilepsy

## Investigations

- Serum glucose & electrolytes: Not routine
- Lumbar puncture (CSF):
  - **Recommended** in children < 12 months (& **considered** in ages 12-18 months)
  - If there is any doubt about the presence of CNS infection
- EEG: is indicated in **atypical** cases
- Imaging (CT): is indicated in **atypical** cases (specially focal neurological signs)

## Prognosis

- ☒ **Excellent**
- ☒ **Incidence of epilepsy = 1%** (in simple febrile seizures)
- ☒ **Factors associated with ↑↑ risk of Epilepsy (9%):**
  - +Ve family history of epilepsy
  - Complex febrile seizures
  - Onset < 12 months
  - Delayed developmental milestones
  - Abnormal neurological examination
  - Recurrent febrile seizures

## Treatment

- A, B, C (*See before*)
- Diazepam IV or rectal (0.3-0.5 mg/Kg/dose)
- Antipyretics e.g., Paracetamol (10-15 mg/Kg/dose), ibuprofen (10-15 mg/Kg/dose)
- Fomentation using tap water (Avoid iced water)
- Identify the cause of fever (Tonsillitis, rash...)
- Treatment of the cause: Antibiotics for tonsillitis
- Prophylactic therapy for prevention of recurrent febrile seizures is controversial & no longer recommended for most children (Na valproate or phenobarbitone)
- Oral diazepam may be used at the onset of each febrile illness for 2-3 days to prevent recurrence
- Treatment of iron-deficiency anemia

## Differential Diagnosis

### **Causes of fever & convulsions:**

- Febrile Convulsions
- CNS infection
- Toxic convulsions (Shigella, Salmonella...)
- Seizures precipitated by fever

## SELECTED EPILEPSY SYNDROMES BY AGE OF ONSET

<b>Neonatal period</b>	
Benign familial neonatal seizures (BFNS)	
Early myoclonic encephalopathy (EME)	Onset in the 1 <sup>st</sup> 2 mo with myoclonic <b>or</b> tonic seizures & EEG burst suppression
Early epileptic encephalopathy (Ohtahara syndrome)	
<b>Infancy</b>	
Infantile spasms (West syndrome)	
Benign infantile seizures	
Benign myoclonic epilepsy of infancy (MEI)	
Severe myoclonic epilepsy of infancy (Dravet syndrome)	Onset in the 1 <sup>st</sup> yr with "febrile seizures" Then with lower or no fever
<b>Childhood</b>	
Benign childhood epilepsy with centrotemporal spikes	
Benign epilepsy with occipital spikes	
Epilepsy with myoclonic absences	
Lennox-Gastaut syndrome	
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), including Landau-Kleffner	
Childhood absence epilepsy (CAE)	
<b>Adolescence</b>	
Juvenile absence epilepsy (JAE)	
Juvenile myoclonic epilepsy (JME)	
Epilepsy with generalized tonic-clonic seizures only	
Progressive myoclonus epilepsies (PME)	
<b>Age-related</b>	
AD nocturnal frontal lobe epilepsy (ADNFLE)	
Familial temporal lobe epilepsies	
AD partial epilepsy with auditory features	
Generalized epilepsies with febrile seizures plus (GEFS+)	AD with early childhood onset
Reflex epilepsies	
Visual sensitive epilepsies	
Primary reading epilepsy	
Startle epilepsy	
<b>Epileptic Encephalopathies</b>	
Early myoclonic encephalopathy (EME) & Ohtahara	
West	
Lennox-Gastaut syndrome & CSWS	
<b>Not traditionally diagnosed as epilepsy</b>	
Benign neonatal seizures (BNS)	
Febrile seizures (FS)	

# Epileptic Seizures

## Definition

The occurrence of  $\geq 2$  **unprovoked** seizures at interval  $\geq 24$  hrs

## Incidence

3 %

## Classification

### A) International

Partial (Focal) Seizures (40%)	Generalized Seizures (60%)
<b>A) Simple partial</b> (Intact consciousness) <ul style="list-style-type: none"> <li>• Motor</li> <li>• Sensory</li> <li>• Autonomic</li> <li>• Psychic</li> </ul> <b>B) Complex partial</b> (Impaired consciousness) <ul style="list-style-type: none"> <li>• Consciousness impaired following SPS</li> <li>• Consciousness impaired at the onset</li> </ul> <b>C) Partial seizures with 2ry generalization</b>	<b>A) Absence seizures</b> (Petit mal) <b>B) Tonic-clonic</b> <b>C) Tonic</b> <b>D) Clonic</b> <b>E) Myoclonic</b> <b>F) Atonic</b> <b>G) Infantile spasm</b>
<b>Unclassified Seizures</b>	

### B) Classification by syndrome (more simple)

- Seizures can be classified into syndromes according to
- It is important in determination of Rx & prognosis
- Many epileptic syndromes are known:
  - Infantile spasm (West syndrome)
  - Lennox-Gastaut syndrome
  - Juvenile Myoclonic Epilepsy (Janz Syndrome)
  - Lafora syndrome (Progressive Myoclonic Epilepsy)
  - Febrile convulsions
  - Benign partial epilepsy with centrotemporal spikes (Rolandic epilepsy)
  - Rasmussen encephalitis
  - Landau-Kleffner syndrome

- Age of onset
- Cognitive development
- Neurological examination
- Seizure type
- EEG picture

## Diagnosis of Epilepsy

### A) History

### B) Examination

### C) Investigations

- Glucose, Na, Ca, Mg: in ALL cases
- Metabolic screen
- Lumbar puncture (CSF): if there is any doubt about the presence of CNS infection
- CT or MRI
  - Focal neurological sign or  $\uparrow\uparrow$  ICT
  - Seizure: CPS, increasing severity & frequency or changing pattern
- EEG: is indicated with the 1<sup>st</sup> **unprovoked** seizure
  - Routine
  - Special lead placement: zygomatic leads
  - Activation procedures: hyperventilation, eye closure, photic stimulation, sleep deprivation
  - Prolonged EEG with video recording

Abnormal EEG during a clinical seizure is **diagnostic** of epilepsy

Normal EEG does **NOT** exclude epilepsy

Interictal EEG is **normal** in 40% of cases

# Partial Seizures

## Definition

Seizures starting in one part of the body (with or without loss of consciousness)

## Types of Partial Seizures

- SPS
- CPS
- Partial seizures with 2ry generalization
- Benign epilepsy syndromes with partial seizures
- Severe epilepsy syndromes with partial seizures

## Simple Partial Seizures

### Pre-ictal

- Aura (30%): Epigastric discomfort, visual, sensory...

### Ictal (Motor\*)

- Tonic or clonic involving one part of the body
- Jacksonian march from the face to arm to leg often occur
- Adversive head turning & conjugate eye movements to the contralateral side may occur
- Consciousness: **Intact** (may talk!!)
- Duration: 10-20 sec
- Automatism: Absent

### Other forms of SPS:

**Sensory:** pain & parasthesia  
**Autonomic:** Nausea, vomiting, palpitation, flushing, cyanosis  
**Psychic:** Smell, taste, emotion

### Post-Ictal

- Todd's paralysis (Neuronal exhaustion)

## Complex Partial Seizures

### Pre-ictal

- Aura (30%): Epigastric pain, tingling, visual, auditory, olfactory, experiential (*Déjà vu*)

### Ictal (Seizure form)

- Staring (Detached)
- Consciousness: impaired (following SPS or impaired at the onset)
- Automatism (= *Automatic repetitive movements*):
  - Alimentary: Chewing, swallowing, lip smacking
  - Automatic behavior: Picking clothes, rubbing objects, non-directive walking
- Tonic or clonic involving one part of the body
- Adversive head turning & conjugate eye movements may occur
- Duration: few minutes

### Post-Ictal

- Sleepiness, transient weakness, amnesia (Can not recall the event)

## Investigations

- EEG: Epileptogenic discharge (Spikes) from the involved lobe (Sleep-deprived EEG\*)
- Still 20% have normal interictal EEG
- MRI: can show lesions (Hamartoma, tumors, temporal lobe sclerosis)

## Partial Seizures with 2ry generalization

Progression of partial seizures into generalized tonic-clonic convulsions

## **Benign epilepsy syndromes with partial seizures**

### **Benign childhood epilepsy with centrotemporal spikes (=Rolandic)**

- Age: School-aged children (6-12 yrs)
- Seizure form: Parasthesia & tonic or clonic contraction of one side of the face associated with ↑↑ salivation & dysphagia ± Ipsilateral parasthesia & clonic convulsions of UL & LL
- Seizures occur during sleep (75%)
- Consciousness: Usually **Intact**
- EEG: Centrotemporal spikes
- Prognosis: Excellent [Usually single or infrequent\*]
- Rx (in frequent cases): Carbamazepine (*Tegretol*)

### **Benign epilepsy with occipital spikes**

**AD nocturnal frontal lobe epilepsy** Linked to Ach receptor gene mutation

**Benign infantile seizures: Familial & Non-familial**

## **Severe epilepsy syndromes with partial seizures**

### **Rasmussen encephalitis**

- Etiology: Auto-antibodies that stimulate glutamate receptors (? CMV infection)
- C/P: Unilateral intractable partial seizures or continuous (*Epilepsia partialis continua*) with progressive hemiparesis
- EEG: Diffuse brain insult with slow background activity
- Prognosis: Poor [potentially lethal or significant neurological deficits]

## **Generalized Seizures**

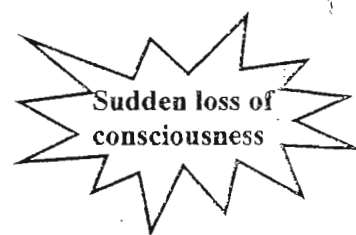
### **Definition**

Seizures involving the whole body at the onset of convulsions

### **Absence Seizures**

#### **a. Typical absence seizures [Petit-mal epilepsy]**

- Age: 5-8 yrs
- No aura, No post-ictal feature, No loss of muscle tone
- Seizure form: Sudden loss of consciousness & cessation of activity
- Frequency: 5-30/day (may be up to 200/day)
- Duration: Few seconds (< 30 sec)
- Precipitated by hyperventilation
- EEG: Generalized spikes (3 Hz spike & slow wave discharges)



<b>Ethosuximide</b> <b>Na Valproate</b>
--

#### **b. Atypical absence seizures**

- Absence + Myoclonic seizures + EEG (1-2 Hz spike & slow wave discharges)

#### **c. Juvenile absence seizures:**

- Later age (10-12 yrs) + EEG (4-6 Hz spike & slow wave discharges) + JME

## **Generalized tonic-clonic seizures** (Grand Mal epilepsy)

It is the most common type (De novo or following partial seizures)

It is characterized by the presence of 3 stages:

- a. **Aura:** Motor, sensory, autonomic or psychic [Warning]
- b. **Seizures**
  - ☒ **Sudden loss of consciousness**
  - ☒ **Tonic phase:** Falling to the ground, apnea, cyanosis
  - ☒ **Clonic phase:** Rhythmic muscle contraction & relaxation,  
Loss of sphincter control & tongue biting
- c. **Post-ictal:** Headache, lethargy & paralysis (Todd's paralysis) "neuronal exhaustion"

## **Benign generalized epilepsies**

Petit mal epilepsy

Benign myoclonic epilepsy of infancy

Juvenile myoclonic epilepsy (Janz syndrome)

Febrile seizures plus syndrome

## **Severe generalized epilepsies**

Early myoclonic encephalopathy

Early epileptic encephalopathy (Ohtahara syndrome)

Lennox-Gastaut syndrome

Progressive myoclonic epilepsy

West syndrome

## **Infantile Spasm** (West syndrome)

### **Etiology**

1. **Idiopathic (Cryptogenic)**
2. **Symptomatic\* (80%)**
  - ☒ **Prenatal:** Congenital infection, Congenital anomalies, Radiation
  - ☒ **Natal:** HIE, birth injury
  - ☒ **Postnatal:** CNS infection (meningitis), trauma, ICH, ↓↓ G, ↓↓ Na, ↑↑ Na, kernicterus

### **Seizure form**

- Onset: Infancy
- Type: Symmetrical contractions of neck, trunk & extremities
- Tendency to occur in clusters, shortly after getting up from sleep
- 3 types: Flexor, extensors or mixed spasms

### **EEG**

Hypsarrhythmia (Irregular high-voltage EEG)

### **Treatment**

- ☒ ACTH
- ☒ Steroids
- ☒ Vigabatrin (specially useful in TS)

**DD: Startles**

### **Pathogenesis**

Stress  
(Developing Brain)  
↓  
↑↑ CRH

## **Landau-Kleffner Syndrome**

Age ≈ 5yrs + Seizure disorder + Loss of language skills & aphasia (DD: Autism)

# Myoclonic Epilepsy of Childhood

## Definition

Disorders characterized by repetitive seizures consisting of brief muscular contractions with loss of body tone & falling forward (Myoclonus)

Disease	Benign Myoclonus of Infancy	Typical Myoclonic Epilepsy of Early Childhood	Complex Myoclonic Epilepsies	Juvenile Myoclonic Epilepsy (Janz Syndrome)	Progressive Myoclonic Epilepsy
Onset	Infancy	6 months-4 yrs	1 <sup>st</sup> year	12-18 yrs	10-18 yrs
Perinatal History	Normal	Normal	HIE	Normal	Normal
Milestones	Normal	Normal	Delayed	Normal	MR within the 1 <sup>st</sup> yr
Seizures	Clusters of Myoclonic seizures	Myoclonic seizures Tonic-clonic seizures	<ul style="list-style-type: none"> <li>1<sup>st</sup>: Tonic-clonic</li> <li>Then: Myoclonic seizures</li> </ul>	<ul style="list-style-type: none"> <li>1<sup>st</sup>: Myoclonic seizures</li> <li>Then: Tonic-clonic</li> <li>Juvenile absence</li> </ul>	<ul style="list-style-type: none"> <li>1<sup>st</sup>: Tonic-clonic</li> <li>Then: Progressive Myoclonic seizures</li> </ul>
EEG	Normal	Fast spike wave complexes Normal background rhythm	Slow spike wave complexes	Irregular spike wave complexes	Polyspike wave Slow background rhythm
Family H (Genetics)	-	1/3 have +ve family history	No	Yes (6p)	Lafora: (6p)
Rx	No Rx			Na Valproate	
Prognosis	Spontaneous resolution	Favorable (learning & language problems)	Poor (MR, refractory seizures)	Relatively good	Poor (MR, cerebellar ataxia)

### Etiological classification of myoclonus:

- Physiological (anxiety, sleep, exercises)
- Epileptic
- Hypoxia, Trauma, infection
- Metabolic: CRF, LCF, Dialysis
- Neoplastic: Neuroblastoma
- Idiopathic torsion dystonia, Hallervorden-Spatz
- Wilson

### Lennox-Gastaut syndrome:

- Triad of:
- MR
  - EEG (Slow spike waves)
  - Seizures (various types)

### Causes of Progressive Myoclonic Epilepsy:

- Lafora disease
- MERRF
- Ceroid lipofuscinosis
- Sialidosis type 1
- Gaucher (Type 3)

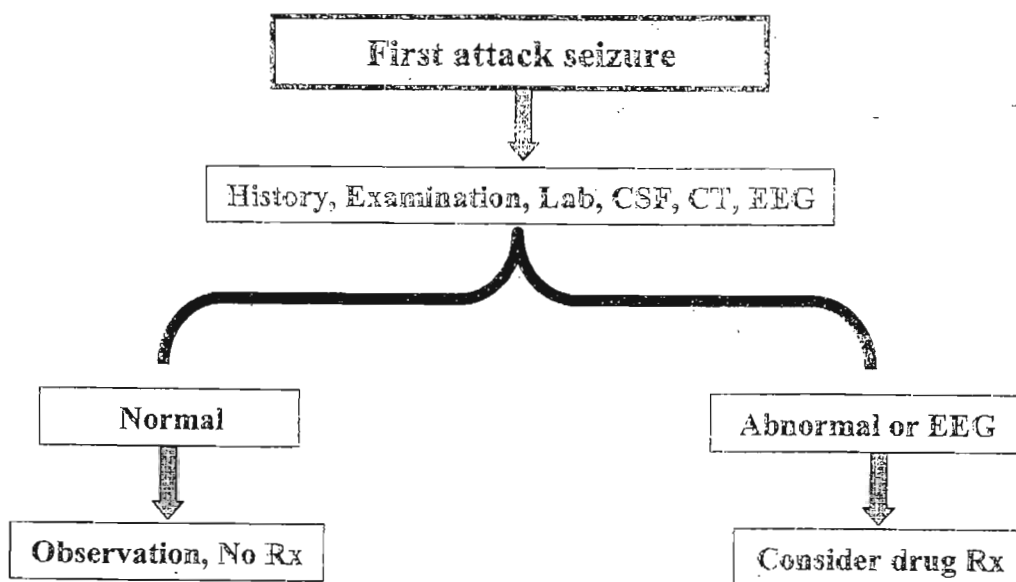


# Treatment of Epilepsy

## A) Anti-epileptic drugs

### General principles

- Anticonvulsant Rx is **not** indicated after a 1<sup>st</sup> unprovoked seizure with **normal** EEG & MRI
- Other considerations: Motor vehicles driving, compliance...
- Treatment should be **individualized**
- The drug of choice depends on the classification of the seizure
- Start with one drug with gradual ↑↑ of the dose until seizure control
- Goal: Control with 1 drug (**monotherapy**), but some may need multiple drugs (**polytherapy**)
- In non-emergency situations: Start with the maintenance dose (without loading)
- Some drugs require more gradual initiation of the dose (Topiramate, carbamazepine)
- **Baseline laboratory studies** including CBC, platelets, liver enzymes, KFTs and UA are often obtained and repeated periodically
- Monthly blood screening is recommended specially in the 1<sup>st</sup> 3 months of Rx, why?
- Duration of anticonvulsant therapy: seizure-free for 2 years (if there is no risk factors)
- Risk factors: age > 12 yrs, neurological dysfunction, frequent seizures before control
- **Weaning** process should occur over 3-6 months, why?
- Indications of serum drug level:
  - At the onset (?therapeutic level)
  - Non-compliant patients
  - Hepatic or renal disease
  - Polytherapy (drug interaction)
  - Symptoms of drug toxicity
  - Change of seizure type
  - Uncontrolled seizures
  - Status epilepticus
- **Mechanism of action of AEDs:** ↓↓ excitability by interfering with the Na or Ca channels
  - Activation of GABA<sub>A</sub> receptors [Phenobarbitone, phenytoin, topiramate]
  - Decrease Glutaminergic transmission [Felbamate]





## Common anticonvulsants

	Indications	Dose	Side Effects
Phenobarbital	G.Tonic-clonic Partial Status epilepticus	L: 20 mg/Kg/day M: 3-8 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ ↓↓ Cognitive function</li> <li>▪ Irritability, sleep disturbances</li> <li>▪ Liver toxicity</li> </ul>
Phenytoin			<ul style="list-style-type: none"> <li>▪ Gum hypertrophy, Generalized LN</li> <li>▪ Aplastic anemia,</li> <li>▪ Ataxia, nystagmus</li> <li>▪ Vit. D deficiency, hirsutism</li> <li>▪ Pregnancy: Teratogenic, bleeding</li> </ul>
Carbamazepine	Partial G.Tonic-clonic	10-30 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Aplastic anemia, Ataxia</li> <li>▪ Liver dysfunction</li> </ul>
Oxcarbazepine		10-30 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Somnolence, dizziness, headache</li> </ul>
Na Valproate	Broad-spectrum	10-40 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Hepatotoxicity, ↓↓ HME</li> <li>▪ Anorexia, weight gain, alopecia</li> <li>▪ 2ry carnitine deficiency</li> </ul>
Vigabatrin	Infantile spasm	30 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Visual field deficits</li> <li>▪ Optic atrophy &amp; retinopathy</li> </ul>
Topiramate	Refractory CPS Adjuvant Rx	1-9 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ ↓↓ Cognitive function, fatigue</li> <li>▪ Glaucoma, weight loss</li> </ul>
Tiagabine	Refractory CPS	6 mg tid	<ul style="list-style-type: none"> <li>▪ ↓↓ Attention span</li> <li>▪ Fatigue</li> </ul>
Gabapentin	Adjuvant Rx	30 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Weight gain, nystagmus, aggression</li> <li>▪ Hyperactivity</li> </ul>
Clonazepam	Adjuvant Rx	0.05-0.2 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Sedation, drowsiness</li> <li>▪ Behavioral changes, ↑↑ salivation</li> </ul>
Ethosuximide	Absence	20-40 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Leukopenia</li> <li>▪ Liver dysfunction</li> </ul>
Lamotrigine	Adjuvant Rx	2-5 mg/Kg/day Use lower dose with...	<ul style="list-style-type: none"> <li>▪ Rash</li> <li>▪ Stevens-Johnson</li> <li>▪ Toxic epidermal necrolysis</li> </ul>
Levetiracetam		20-40 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Behavioral changes</li> <li>▪ Somnolence</li> </ul>
Felbamate		15-45 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Liver toxicity (serious)</li> </ul>
Primidone		10-20 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Liver toxicity</li> </ul>
Zonisamide		4-8 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Dizziness, ataxia</li> </ul>
Rufinamide		30-40 mg/Kg/day	<ul style="list-style-type: none"> <li>▪ Somnolence</li> </ul>
ACTH	Infantile spasm	20 units /day IM	<ul style="list-style-type: none"> <li>▪ HTN</li> <li>▪ ↑↑ glucose</li> </ul>

## Choice of Drug Therapy

### 1. Comparative effectiveness

Type	Therapy
Partial seizures	Carbamazepine, Oxcarbazepine
BCECT	None or Carbamazepine, Oxcarbazepine
Childhood absence epilepsy	Ethosuximide, Valproate
Lennox-Gastaut syndrome	Valproate, Lamotrigine, Topiramate
Juvenile myoclonic epilepsy	Valproate, Lamotrigine, Topiramate
Benign myoclonic epilepsy	Valproate
Infantile spasms	ACTH, Vigabatrin
Pyridoxine-dependent epilepsy	Pyridoxine (100 mg/day)
Cerebral folate deficiency	Folic acid

### 2. Potential for paradoxical seizure aggravation

Phenytoin & carbamazepine are contraindicated in absence, myoclonic seizures

### 3. Comparative tolerability: ↑↑ risk of liver toxicity for valproate in children <2 yr, on polytherapy & with metabolic disorders

### 4. Cost and availability

### 5. Ease of initiation: Medications that are started very gradually such as lamotrigine and topiramate may not be chosen if there is a need to achieve a therapeutic level quickly

### 6. Drug interactions

- Enzyme inhibitors (e.g., valproate) ↑↑ levels of lamotrigine, phenobarbital
- Enzyme inducers (e.g., phenobarbital, phenytoin) ↓↓ levels of lamotrigine, valproate

### 7. Comorbid conditions:

- Migraine: Valproate or topiramate
- Obese patients: Valproate might be avoided, topiramate might be used instead

### 8. Coexisting seizures: [Absence & generalized tonic-clonic seizures??]

### 9. History of prior response to specific AEDs

### 10. Ease of use: Drugs given once or twice a day & palatable liquid preparation

### 11. Patient's and family's preferences

### 12. Mechanism of drug action: Avoid use of drugs sharing the same mechanism of action

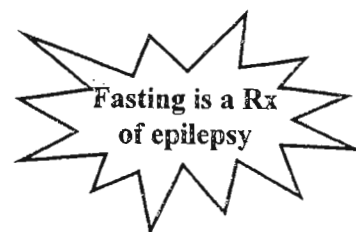
### 13. Genetics and genetic testing: Some side effects are related to certain HLA alleles

### 14. Teratogenic profiles

- Valproate and carbamazepine: Spina bifida
- Carbamazepine phenytoin and phenobarbital: cardiac malformation and cleft palate.

## B) Ketogenic Diet

- Fasting is a treatment of epilepsy
- Ketogenic diet: fats 70%, CHO 20%, proteins 10%
- Avoid ketogenic diet if Na valproate is concomitantly used



## C) Surgery

- Indications:
  - Intractable seizures
  - Localized focus
- Procedures:
  - Focal resection
  - Hemispherectomy (Hemidecortication)
  - Interhemispheric commissurotomy
  - Temporal lobectomy
- Localization of the lesion:
  - EEG (routine, special leads, with video recording & intra-operative)
  - Imaging: CT, MRI, fMRI, SPECT, PET, MEG (magnetoencephalography)

## D) Vagal Nerve Stimulation

## E) Counseling

- The child should be treated as normal (sleeping alone)
- Parent education about etiology, medications (dose & side effects), prognosis...
- No restriction of physical activity
- Some activities should be attended (swimming...)
- **Individual consideration** remains the basic determinant
- ↑↑ risk of mortality (2 or more folds): underlying disease & poor seizure control

Sports Type	Consideration
Body contact sports	physician evaluation of benefits and risks
Noncontact sports	Anxiety and fatigue can cause a problem in some children
Gymnastics	A fall (parallel bars, rope climbing) therefore should be avoided
Swimming	Under supervision Competitive underwater swimming should be discouraged

## F) Additional therapy

- IVIG: in West, lennox-Gastaut, Landau-Kleffner

# Status Epilepticus

## Definition

- ☒ **Status epilepticus:** Convulsive fit lasting for > 30 minutes OR short repetitive fits without regaining consciousness in between
- ☒ **Refractory status epilepticus:** Status epilepticus not responding to 1<sup>st</sup> line Rx
- ☒ **Impending status epilepticus:** Seizures between 5-30 minutes
- ☒ **Convulsive status epilepticus:**
- ☒ **Non-convulsive status epilepticus:** Confusion, dementia, absence
- ☒ **New-onset refractory status epilepticus:** No prior epilepsy, unknown etiology

## Incidence

- Status epilepticus occur in 10% of children with epilepsy
- Status epilepticus may be the 1<sup>st</sup> presentation of epilepsy (30%)

## Etiology

1. Prolonged febrile convulsions
2. Acute brain insult (Causes of...)
3. Status Epilepticus in an epileptic patient
  - Noncompliant patients
  - Sudden withdrawal of antiepileptics
  - Fever

## Pathophysiologic Changes

### A) Electromechanical changes

- Electrical activity (EEG) & motor response (convulsions) are usually associated
- E/M dissociation occurs with prolonged convulsions (> 1 hr), muscle paralysis (Pancuronium)

### B) Cerebral changes

- Cerebral blood flow ↑↑ by 900 %
- Cerebral O<sub>2</sub> consumption ↑↑ by 300 %

### C) Systemic changes

- CNS: Ischemia, Hemorrhage, edema, ↑↑ ICP
- Respiratory: Airway obstruction, apnea, aspiration, pulmonary edema
- CVS: Shock, HF, HTN
- Metabolic: Hyperpyrexia, metabolic acidosis, ↓↓ glucoses, ↓↓ Na, ↑↑ K

## Management of Status Epilepticus

### Immediate Management

#### 1. Airway

- Check patency of airway (Keep the patient on his side + oropharyngeal airway)
- Removal of FB & gentle suction

#### 2. Breathing

- Oxygen therapy is mandatory (Cerebral ischemia)
- Mechanical ventilation may be required

#### 3. Circulation

- Establish a vascular access
- Withdraw blood sample for investigations (Glucose, Na, Ca, Mg)
- Correction of shock, hypoglycemia & maintenance of BP

## Initial Anticonvulsant Therapy

1. **Lorazepam** (IV or intranasal 0.1 mg/Kg)
2. **Midazolam** (IV, IM, Buccal or intranasal 0.2 mg/Kg)
3. **Diazepam** (Neuril 10 mg/2 ml)
  - Dose: 0.3-0.5 mg/Kg/dose. Maximum dose = 10 mg/dose. Maximum = 3 doses
  - Route: IV (rectal route can be used) or diazepam rectal gel
  - Precaution: Slow IV (over 3-5 minutes)
  - Side effects: ↓↓ RC, Hypotension
4. **Phenobarbital** (Somnialetta 40 mg/1 ml)
  - Dose: Loading = 15-20 mg/Kg/dose  
Maintenance = 3-8 mg/Kg/day
  - Route: IV
  - Precaution: Slow IV (over 3-5 minutes)
  - Side effects: ↓↓ RC
5. **Phenytoin** (Epanutin 250 mg/5 ml)
  - Dose: Loading = 15-20 mg/Kg/dose  
Maintenance = 3-8 mg/Kg/day
  - Route: IV
  - Precaution: Slow IV (over 10-15 minutes)
  - Side effects: Hypotension, bradycardia, HB, arrhythmias

**Phosphenytoin**

**Phenytoin should be diluted in NS not glucose**

## Management of Refractory Status epilepticus

1. **Diazepam constant infusion** (Neuril 10 mg/2 ml)
  - Dose: 0.2-0.3 mg/Kg/hr (2-3 mg/hr)
  - Practical dose = 10 mg + 200 cc NS → infusion rate (40-60 cc/hr)
2. **Midazolam constant infusion** (Dormicum 5 mg/1ml)
  - Dose: 0.1-0.2 mg/Kg/hr
3. **High dose Phenobarbital**
4. **Thiopental** (Thiopental 500 mg/10 ml)
  - Dose: Loading = 2-4 mg/Kg/dose IV  
Maintenance = Titration (Clinical & EEG burst suppression)
  - Duration: 48 hrs
  - Mechanism: Barbiturate coma
  - Requirements: ICU + Mechanical ventilation + EEG monitoring
5. **Na Valproate IV**: is now available
6. **General anesthesia** (Halothane & isoflurane)
7. **Paraldehyde**
  - Dose: Loading = 150-200 mg/Kg/dose (IV)  
Maintenance = 20 mg/Kg/hr (IV infusion)
  - Precaution: Use 5 % solution & glass bottle
8. **Lidocaine** (Xylocaine 1 g/50 ml)
  - Dose: Loading = 1-2 mg/Kg/dose (IV)  
Maintenance = 2 mg/Kg/hr (IV infusion)
  - Side effects: Hypotension, HB, convulsions

**Barbiturate Coma**

## After Seizure control

Maintenance anticonvulsant therapy (Duration is controversial ≈ 3 months in 1<sup>st</sup> attack)

# Conditions that Mimic Seizures

## Definition

Conditions sharing common features with seizures (DCL, cyanosis, abnormal movements)

## Classification

- A. Generalized paroxysms
- B. Abnormal movements & postures
- C. Oculomotor abnormalities
- D. Sleep-related disorders

## **A. Generalized Paroxysms**

### 1. Apnea

### 2. Benign paroxysmal vertigo

- Age: 1-3 yr
- C/P: Attacks of vertigo, ataxia, nystagmus, nausea & vomiting  
Normal neurological examination, No loss of consciousness, Normal EEG
- Rx: Diphenhydramine

### 3. Breath-Holding Spells

	a. Cyanotic spells	b. Pallid spells
Frequency	More common	Less common
Age peak	6 months-5 yrs	
Mechanism	Expiratory apnea leading to cyanosis	Reflex vagal-cardiac bradycardia
Clinical Picture	The spell is always provoked by upsetting the child (crying)	The spell is always provoked by painful stimulus (Head trauma)
	Apnea, cyanosis, loss of consciousness (lifeless) Reflex anoxic seizures may occur	
EEG	Normal	
Rx	Reassurance Rx of coexisting iron deficiency is needed	
Prognosis	Self-limited, outgrown within a few years	

### 4. Cardiac syncope "Long QT interval"

### 5. Alice in Wonderland Syndrome: Transient distortion of body image or visual images

### 6. Pseudoseizures (= Psychogenic non-epileptic seizures)

- Age & sex: ♀ 10-18 yrs (neurotic personality\*)
- C/P:
  - Simulation of seizures by the patient
  - Secondary gain is usually found
  - Clinical manifestations do not coincide with organic epilepsy
  - ↑↑ with attention & audients
  - No cyanosis, No incontinence, No injury, No tongue biting
- Diagnosis: By exclusion (video-EEG monitoring is helpful)
- Rx: Psychotherapy

## B. Abnormal Movements & Postures

### 1. Neonatal Jitteriness

### 2. Benign paroxysmal torticollis

- Age: Infancy (< 3 months)
- C/P: Attacks of head tilt + nausea & vomiting  
Normal neurological examination, No loss of consciousness, Normal EEG
- Rx: Spontaneous resolution < 5 yrs

### 3. Sandifer Syndrome (GERD)

- Attacks (*30 min after meals*) of stiffening and opisthotonus ± apnea & staring

### 4. Familial paroxysmal choreoathetosis

- Age: 8-14 yrs
- C/P: Attacks (< 1 minute) of choreoathetosis precipitated by sudden movement, startle or change of position
- Normal neurological examination, No loss of consciousness, Normal EEG
- Rx: Phenytoin

### 5. Motor tics

### 6. Episodic Ataxias (7 types are described)

- Type 1 (mutation in K channel): Brief episodes (seconds to minutes) of cerebellar ataxia
- Type 2 (mutation in Ca channel): Longer attacks (minutes to hours) of cerebellar signs

### 7. Shuddering attacks

- Age: 4-6 months
- C/P: Attacks of sudden flexion of the head & trunk with shivering  
Normal neurological examination, No loss of consciousness, Normal EEG

### 8. Hereditary chin trembling (AD)

- Repeated attacks of chin trembling precipitated by stress & frustration
- Normal neurological examination, No loss of consciousness, Normal EEG

### 9. Rage attacks (Dyscontrol syndrome)

- Age: Childhood & adolescence
- C/P: Attacks of violent physical behavior with minimal provocation (Kicking, biting, abusive language) followed by fatigue, amnesia & remorse
- Normal neurological examination, No loss of consciousness, Normal EEG

### 10. Masturbation

- Age & sex: Females 2 month-3 yrs
- C/P: Attacks of tonic posturing with copulatory movements followed by flushing & perspiration
- Causes: Idiopathic\*, sexual abuse, genital abnormalities
- Normal neurological examination, No loss of consciousness, Normal EEG
- Rx: Spontaneous resolution at 3 yrs

## C. Oculomotor abnormalities

### 1. Spasmus Nutans

- Triad of nystagmus, head tilt (Torticollis), and head nodding
- Brain MRI & EEG: Normal
- Prognosis: Disappear before 5 yr of age

### 2. Daydreaming

- Staring & inattention in bored or tired child
- Responsiveness is maintained

### 3. Opsoclonus myoclonus syndrome (Dancing eyes)

- Continuous, random, irregular, and conjugate eye movements
- Causes: Encephalitis and neuroblastoma

### 4. Oculomotor apraxia

- Difficulty moving the eye, especially with saccade movements



## D. Sleep-related disorders

### 1. Benign sleep myoclonus: Random myoclonic jerks of the limbs

### 2. Sleep transition disorders

- Nocturnal head banging, rolling or body rocking (on trying to fall asleep)
- Spontaneous resolution by 5 yr of age

### 3. Restless leg syndrome:

- Causes leg pain, nocturnal arousals and insomnia

### 4. Night Terrors

	Nightmares	Night terrors
Incidence	Very common	More severe
	REM sleep disorder	NREM sleep disorder
Definition	Attacks of fear & screaming during the last 1/3 of night	Attacks of fear & screaming during the 1 <sup>st</sup> 1/3 of night (12 am-2 am)
C/P	Sudden onset The child screams & appears frightened Sleeps again within minutes	
Autonomic manifestations	Mild or absent	Frequent & prominent (↑↑ HR, ↑↑ Ventilation, dilated pupils)
Arousal threshold	Low	High
Ability to recall	Can recall vividly (next day)	Can not recall (Total amnesia)

### 5. Narcolepsy-cataplexy syndrome

#### ☒ Narcolepsy

- Sudden irresistible desire to sleep that occurs mainly in adolescents
- Attacks may be short (DD: ADHD) or long (DD: Epilepsy)

#### ☒ Cataplexy

- Transient loss of muscle tone
- No loss of consciousness
- Rx: Amphetamine, methylphenidate & counseling



# **Demyelinating Diseases**

## **Definition**

Degeneration of previously normal myelin (DD: Dysmyelination, hypomyelination)

## **Classification**

<b>ADEM</b>	Clinical event must include encephalopathy (behavioral and/or altered consciousness) New symptoms or signs within 3 months are considered part of same ADEM event
<b>NMO</b>	Must have: ➤ Optic neuritis and transverse myelitis as major criteria ➤ Spinal MRI lesion extending $\geq 3$ segments or NMO-IgG positive
<b>Relapsing CNS inflammatory demyelination</b>	
<b>Recurrent ADEM</b>	New event of ADEM with recurrence of initial ADEM manifestations $\geq 3$ months after initial event and not related to withdrawal of steroids
<b>Multiphasic ADEM</b>	ADEM followed by new clinical event also meeting criteria for ADEM, but involving new CNS lesions (clinically and radiologically)
<b>Pediatric MS</b>	Two or more events separated in time (4 or more weeks) and space. New MRI lesions 3 months or longer after the initial clinical event can be used to satisfy criteria for dissemination in time

# **Neuromyelitis Optica**

**Definition** Demyelinating disorder characterized by ON  $\pm$  transverse myelitis (Rare)

**Pathogenesis** Anti-aquaporin-4 antibodies (NMO antibodies)

## **Clinical Picture**

- Visual (Optic neuritis): Painful vision loss, field or color defect
- Spinal cord: Transverse myelitis
- Other parts of the CNS are free (clinical & radiological)

## **Investigations**

- ☐ CSF: Mild pleocytosis
- ☐ Serum: Anti-aquaporin-4 antibodies

## **Treatment**

- Methylprednisolone: 20-30 mg/Kg/day for 3-5 days+ oral steroids
- Interferon- $\beta$ , Rituximab

**Prognosis** Poor

# Multiple Sclerosis

## Definition

- Chronic demyelinating disorder of the brain, spinal cord & optic nerve characterized by relapsing-remitting course of neurologic episodes separated in time & space
- Rare in children (2-5% of all cases of MS)

## Pathogenesis

- ☐ Genetic + Environmental + Immune dysregulation (T & B cell)
- ☐ Pathology: Demyelination

## Clinical Picture

- Cerebrum: Cognitive impairment, sensory disturbances, weakness or paralysis (UMNL)
- Visual (Optic neuritis): Painful vision loss, scotoma, diplopia
- Brainstem: Diplopia, vertigo, bulbar symptoms (5)
- Cerebellar: Ataxia, tremors
- Spinal cord: weakness, sphincteric (bladder/bowel dysfunction), impotence

## Investigations

- ☐ MRI:
  - Hyperdense white matter lesions (*Site: periventricular, juxtacortical, infratentorial areas*)
  - Gadolinium-enhancing lesion (*Activity*)
- ☐ CSF: Mild pleocytosis, ↑↑ IgG index, Oligoclonal bands
- ☐ Evoked potential studies: VEP, ABR

The principle is to establish dissemination in time & space

## Diagnosis

- ☐ ≥ 2 demyelinating episodes (clinical evidence of ≥ 2 lesions) separated by > 30 days
- ☐ MRI can substitute 1 of the episodes
- ☐ Dissemination in time by MRI:
  - New MRI lesion ≥ 30 days after the initial event
  - Gadolinium-enhancing lesion ≥ 3 months after the initial event
- ☐ Primary progressive MS: 1 yr progressive deficit & 2 of (MRI brain, MRI spine or CSF)
- ☐ Possible MS: patients having appropriate manifestations but not satisfying criteria

## Treatment

- Methylprednisolone: 20-30 mg/Kg/day for 3-5 days ± oral steroids
- DMT: Interferon-β, natalizumab

## Prognosis

- Irreversible disability in 20-30 yrs

# **Acute Disseminated Encephalomyelitis**

## **(ADEM)**

### **Definition**

- Acute demyelinating disorder with multifocal neurologic deficits
- Typically accompanied by encephalopathy (behavioral and/or altered consciousness)
- Peak age: 5-8 yrs

### **Pathogenesis**

- ☐ Immune-mediated triggered by molecular mimicry
- ☐ Postinfectious: Influenza, CMV, EBV, varicella, HSV, MMR
- ☐ Postvaccination: MMR, DPT, rabies, influenza

### **Clinical Picture**

- Constitutional manifestations: Fever, headache, lethargy, vomiting
- Encephalopathy, seizures, meningeal signs
- Focal neurological signs are difficult to be assessed, why?
  - Motor (UMNL), sensory disturbances
  - Visual loss, ataxia
  - Sphincteric (bladder dysfunction, constipation)



### **Investigations**

- ☐ MRI: Large multifocal high signal T2 lesions (*Site: white & gray matter*)
- ☐ CSF: Mild pleocytosis, ↑↑ protein
- ☐ EEG: Generalized slowing

### **Treatment**

- Methylprednisolone: 20-30 mg/Kg/day for 5 days + oral steroids (*for 1 month*)
- Other lines: IVIG (2 g/Kg over 2-5 days) or Plasmapheresis: 5-7 sessions

**Prognosis** Many (complete recovery), some (residual deficit), recurrent (DD: MS)

### **Differential Diagnosis**

- ☐ Encephalopathy: Metabolic, mitochondrial, tumor, leukodystrophy...
- ☐ MS

	<b>ADEM</b>	<b>MS</b>
Age	<10 yr	>10 yr
Stupor/coma	+	-
Fever/vomiting	+	-
Family history	No	20%
Sensory complaints	+	+
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
MRI imaging	Widespread lesions: Gray & white	Isolated lesions: white matter
CSF	Pleocytosis (lymphocytosis)	Oligoclonal bands
Response to steroids	+	+
Follow-up	No new lesions	New lesions

# Movement Disorders

## Ataxia

### Definition

Incoordination of voluntary movements in absence of weakness or paralysis

### Types

- |                |               |             |
|----------------|---------------|-------------|
| 1. Cerebellar* | 3. Vestibular | 5. Combined |
| 2. Sensory     | 4. Hysterical |             |

### Physiological Background

Cerebellum is formed of:

- ☒ Archicerebellum (Vestibulo-cerebellum): Equilibrium
- ☒ Paleocerebellum (Spino-cerebellum): Muscle tone
- ☒ Neocerebellum (Cerebro-cerebellum): Coordination

**Cerebellum receives afferent fibers from:**

- 1. Proprioceptors
- 2. Visual receptors
- 3. Vestibular apparatus??

## Sensory Ataxia

### Definition

Ataxia due to loss of proprioceptive sensations (Deep sensation)

### Etiology

1. Peripheral nerves: Polyneuropathy
2. Posterior root: Tabes dorsalis
3. Posterior column:
  - Subacute combined degeneration of the spinal cord [Vitamin B<sub>12</sub> deficiency]
  - Friedreich's ataxia [Cerebellum + 3 P]
4. Thalamic lesions
5. Cortical sensory loss: Parietal lobe lesions

### Clinical Picture

- Kinetic tremors occur only on eye closure (e.g., finger-to-finger test...)
- +Ve Romberg's sign
- Deep sensory loss
- Stamping gait
- Hypotonia & hyporeflexia

## Vestibular Ataxia

### Definition

Ataxia due to lesions of the vestibular system (SCC, utricle & saccule)

### Etiology

- |                     |                        |
|---------------------|------------------------|
| 1. Labyrinthitis    | 3. Vestibular neuritis |
| 2. Acoustic neuroma | 4. Vascular diseases   |

### Clinical Picture

- Ataxia
- Vertigo
- Nystagmus
- Tinnitus & deafness
- +Ve caloric test

# Cerebellar Ataxia

## Clinical Picture

### A) Gait

- Archicerebellar lesions: Wide-base (drunken gait)
- Neocerebellar lesions: Deviation to the same side (**Unilateral**) or zigzag (**bilateral**)

Manifestations of Cerebellar ataxia occur on the **same** side of the lesion

### B) Hypotonia & Hyporeflexia (Pendular knee reflex)

### C) Incoordination of voluntary movements

- Nystagmus (Horizontal\*)
- Staccato speech
- Head nodding & trunk titubation
- Kinetic tremors
- Decomposition of movements
- Dysmetria (Hypometria or Hypermetria)
- Dysdiadokokinesia
- Rebound phenomenon

#### Clinical tests:

1. Finger-to-nose
2. Finger-to-finger
3. Finger-to-doctor's finger
4. Buttoning & unbuttoning
5. Supination & pronation
6. Heal-to-knee

## Acute Ataxia

(Recurrent chorea)

## Etiology

### 1. Postinfections/Immune

#### a. Acute postinfectious cerebellitis (varicella)

- Most common cause of acute ataxia
- Age peak = 1-3 yrs
- Preceding viral infection (2-3 wks): VZV, Influenza, enteroviruses
- C/P: Sudden onset & regressive course...
- Diagnosis: Exclusion of other causes, MRI
- Prognosis: Excellent (recovery within 2 months)

Autoimmune

#### b. ADEM

#### c. MS

#### d. Miller-Fisher syndrome: Acute external ophthalmoplegia, ataxia & areflexia

### 2. Infection

- a. Brainstem encephalitis
- b. Cerebellar abscess
- c. Acute labyrinthitis: 2ry to OM

### 3. Toxic

- a. Anticonvulsants: Phenytoin, Carbamazepine
- b. Exogenous toxins: Lead, Alcohol

### 4. Traumatic (Concussion or hemorrhage)

### 5. Neoplastic

### 6. Vascular: Cerebellar Hge

### 7. Migraine

### 8. Genetic disorders

- a. Episodic Ataxias: Types 1 & 2
- b. AD ataxia
- c. Hartnup disease
- d. Maple syrup urine disease

Brain tumors should be excluded in any child with Ataxia

# **Chronic Ataxia**

(Progressive chorea)

## **Etiology**

### **1. Congenital anomalies**

- a. Agensis of the cerebellar vermis
- b. Cerebellar aplasia
- c. Dandy-Walker syndrome
- d. Chiari malformation
- e. Encephalocele
- f. **Joubert syndrome (AR)**
  - Agensis of the cerebellar vermis
  - Ataxia, hypotonia, MR  $\pm$  other anomalies (e.g., NPH) "Joubert-related disorders"
  - MRI: Molar-tooth sign

### **2. Perinatal: Ataxic CP**

### **3. Neoplastic: Astrocytoma, medulloblastoma...**

### **4. Hereditary ataxia**

- a. Ataxia telangiectasia
- b. Friedreich ataxia [Cerebellum + 3 P]
- c. Roussy-Levy Syndrome (HMSN Type 1 + Friedrich's ataxia)
- d. Degenerative brain diseases
  - Gray matter diseases: GM<sub>1</sub>, GM<sub>2</sub>, Gaucher disease
  - White matter diseases: Leukodystrophy (MLD, XL-ALD)

### **5. Metabolic**

- a. Refsum disease
- b. Abetalipoproteinemia (Acanthocytosis)
- c. Vitamin E Deficiency
- d. Gaucher disease (Type 3)
- e. Niemann-Pick disease (Type C)
- f. Hartnup disease: Defect in tryptophan intestinal absorption (Ataxia + Pellagra-like rash)
- g. Maple syrup urine disease
- h. Argininosuccinic aciduria ( $\downarrow\downarrow$  Argininosuccinate lyase):  
[= Urea cycle defect, Hyperammonemia, Ataxia, MR & dry brittle hair]

## **Friedreich's ataxia**

### **Etiology**

AR (Triplet repeat expansion)

### **Pathology**

Degeneration of [Cerebellum + 3 P]

### **Clinical Picture**

1. Cerebellum: Cerebellar ataxia (< 10 yrs)
2. Posterior column: Sensory ataxia (Deep sensory loss)
3. Peripheral nerves: PN (Glove & stockings sensory loss + lost ankle preserved knee reflex)
4. Pyramidal tract: +ve Babinski sign but with Hypotonia, why??
5. Hypertrophic cardiomyopathy: HF is the main cause of death
6. Skeletal: Pes-cavus & kyphoscoliosis

## **Abetalipoproteinemia (Acanthocytosis)**

### **Etiology (AR)**

- ↓↓ Apo B-48 (Intestine) → No chylomicrons → Fat malabsorption (steatorrhea)
- ↓↓ Apo B-100 (Liver) → No VLDL & No LDL (↓↓ serum cholesterol & triglycerides)

### **Clinical picture**

- FTT, steatorrhea, rickets
- Neurological (2<sup>nd</sup> decade): ataxia, PN, deep sensory loss & retinitis pigmentosa
- Hematological: acanthocytes (multiple spiny projections)

**Treatment** Medium-chain triglycerides & Vitamin E, A, D, K

## **Ataxia-Telangiectasia (AR<sup>11</sup>)**

- Combined immunodeficiency
- Cerebellar Ataxia & nystagmus (≈ at 2 yrs)
- Telangiectasia (≈ 3-6 yrs): Dilated BV on the conjunctiva, lateral aspect of the nose, ears
- Chromosomal breakage (Chromosome 14)
- ↑↑ Risk of malignancy (Lymphoma & brain tumors): "100-fold"
- ↓↓ IgA, ↓↓ IgG
- ↑↑ α-Fetoprotein
- Cause of death: Tumors & bronchiectasis

## **Tremors**

### **Definition**

Involuntary, rapid, rhythmic movements mainly involving the hands

### **Etiology**

1. **Benign:** Spasmus nutans, jitteriness, shuddering attacks
2. **Essential tremors (AD):** Rx: Propranolol
3. **Drugs:** Caffeine, theophylline, amphetamine, phenytoin, carbamazepine, alcohol
4. **Neuropathies**
5. **Metabolic:** Hypoglycemia, ↓↓ Ca, ↓↓ Mg,
6. **Endocrinal:** Thyrotoxicosis
7. **Neoplastic:** Hyperadrenergic states (Pheochromocytoma, neuroblastoma)
8. **Recovery from severe head trauma**
9. **Flapping tremors:** Organ failure (renal, hepatic, respiratory)
10. **Hereditary:** Essential tremors, Wilson, Huntington disease, fragile X premutation

## **Jitteriness**

- Rapid, rhythmic tremors of equal amplitude around a fixed axis
- It is normal in healthy neonates

## **Athetosis**

### **Definition**

Involuntary, static, irregular, snake-like movements involving mainly the hands & fingers, aggravated by emotional stress and disappear during sleep

**Etiology** As chorea (usually associated)

**Treatment** Trihexyphenidyl (Parkinol)

# Chorea

## Definition

Involuntary, static, irregular, sudden, jerky, semi-purposeful movements involving mainly the face, trunk & limbs, aggravated by emotional stress and disappear during sleep

## Etiology

1. Rheumatic Chorea\* (Sydenham chorea)
2. Bilirubin encephalopathy (Kernicterus)
3. Wilson disease
4. Lesch-Nyhan syndrome (XL-R)
5. Familial paroxysmal choreoathetosis (= Paroxysmal kinesigenic choreoathetosis)
6. Huntington chorea (AD): Disease of adulthood, rare in children (Anticipation & imprinting)
7. Benign hereditary chorea
8. Chorea gravidarum
9. SLE & APS
10. Infections: Viral encephalitis
11. Postinfectious or postvaccination encephalitis
12. Brain tumors
13. Toxic: INH, OCPs, phenytoin, steroids
14. Organ failure: Hepatic failure, renal failure

## Rheumatic Chorea

(Sydenham chorea)

## Definition

- It is the most common cause of chorea in children
- It the only neurological manifestation of rheumatic fever
- Rheumatic chorea can be the **only** manifestation of rheumatic fever

## Clinical Picture (♀ > ♂)

### A) Chorea

### B) Hypotonia

- Boat-shaped hands: flexion at the wrist + hyperextension at the fingers
- Milk maid grip: relaxation & tightening with hand shaking
- Pronator sign: The arm & palm turn out when held above the head

### C) Typical signs

- Darting tongue: The tongue can not be protruded for longer than few seconds
- Arm extension: Wavy finger movement (Piano-player sign)

### D) Emotional lability

Paralytic chorea (**Chorea mollis**):  
severe weakness & hypotonia

## Treatment

### 1. LAP

### 2. Drug therapy

- Valproate, carbamazepine
- Phenobarbital (3 mg/Kg/day)
- Haloperidol (0.1-0.2 mg/Kg/day)



# Dystonia

## Definition

Involuntary, static, irregular, **twisting**-like movements involving mainly the neck, trunk & proximal muscles of limbs, aggravated by emotional stress and disappear during sleep

## Distribution

1. **Focal:** Single body part (Blepharospasm, writer's cramp, torticollis)
2. **Segmental:**  $\geq 2$  adjacent parts
3. **Hemidystonia:** One side of the body
4. **Generalized**

Dystonia may be considered an abnormal posture rather than abnormal movement

## Etiology

### A. Primary torsion dystonia (Primary generalized dystonia = Dystonia musculorum deformans)

1. DYT1 mutation dystonia: LL dystonia then generalization
2. DYT5 mutation: **Dopa-responsive dystonia** (Segawa syndrome): AD
  - Cause: Dopamine deficiency
  - C/P: Diurnal variation
  - Rx: Dramatic response to levodopa
3. DYT11 (**Myoclonus dystonia**):
  - C/P: Dystonia & myoclonus (Improved with alcohol!!!)

### B. Drug-induced dystonia

- Antiemetics: Metoclopramide (*primperan*)
- Antipsychotics: Chlorpromazine, haloperidol
- Risperidone

Dopamine-blocking agents

### C. CP (Bilirubin encephalopathy): Kernicterus

### D. Metabolic

1. Wilson
2. Lesch-Nyhan syndrome
3. Dopa-responsive dystonia
4. Hallervorden-Spatz
  - Pathology: Excessive iron deposition in the basal ganglia
  - MRI: **Tiger's eye sign**
5. Glutaric aciduria (type1), GM1 gangliosidosis (Type 3)

### E. Other causes:

1. Benign paroxysmal torticollis

## Clinical Picture

- Dystonia
- Abnormal posture (e.g., Tiptoe walking...)
- Difficulties in walking, speech & swallowing

## Treatment

- Trihexyphenidyl (Artane), levodopa
- Local injection of botulinum toxin (focal dystonia)
- Intrathecal baclofen
- Deep brain stimulation (DBS): Leads implanted into BG



# Tics

## Definition

Involuntary, irresistible, purposeless movements; aggravated by emotional stress and disappear during sleep

## Classification

Tics are the most common movement disorder of childhood

### A) Transient tics disorder of childhood\*

- +Ve family history
- Type: blinking, throat-clearing noises, facial or shoulder movements
- Prognosis: Transient lasting for weeks to 1 yr

### B) Chronic motor tics

- -Ve family history
- Prognosis: may persist throughout life

### C) Gilles de la Tourette syndrome: is formed of 4 components

1. Motor tics
2. Obsessive-compulsive behavior
3. Vocal tics: throat-clearing, echolalia, palilalia, coprolalia, echokinesis
4. ADHD

## Treatment

Haloperidol (0.1-0.2 mg/Kg/day)

### Causes of torticollis:

- **Congenital:**
  - Sternomastoid tumor
  - Absent Sternomastoid
  - Vertebral anomalies (Klippel-Feil syndrome, hemivertebra...)
- **Trauma**
- **Tumors:** Posterior fossa
- **Inflammation**
  - Pharyngitis, retropharyngeal abscess
  - Cervical lymphadenitis
  - Osteomyelitis & TB
  - JRA
- **Errors of refraction (Squint)**
- **Neurological:** Dystonia, Wilson, Kernicterus
- **Benign paroxysmal torticollis**



# Transverse Myelitis

## Definition

Acute inflammatory disorder of the spinal cord that evolves in hours or days

## Etiology (Immune-mediated)

- Postinfectious inflammation of the spinal cord (myelitis)
- Preceding infection or vaccines: Viral (VZV, HSV...)

## Pathology

- Myelitis (Thoracic segments\*)
- Demyelination

## Clinical Picture

- Acute onset & progressive course (Maximum deficit: 2 days-2 wks)
- Constitutional manifestations: FAHM
- Back (or neck) pain
- Neurological manifestations:
  - ☒ **Motor:**
    - Weakness or paralysis
    - Paraplegia or quadriplegia (First with flaccidity, then spasticity within weeks)
  - ☒ **Sensory:**
    - Sensory level (usually in the mid thoracic region) below which, all sensations are lost
    - Parasthesia is common
  - ☒ **Sphincteric:**
    - Urine retention
    - Catheterization may be needed

**Neuromyelitis optica** (Devic disease)  
Transverse myelitis +  
Optic neuritis (eye pain & vision loss)

## Investigations

- MRI spine: Fusiform (Thoracolumbar area\*), exclude masses
- CSF: Lymphocyte pleocytosis, ↑↑ IgG index, ↑↑ proteins

## Prognosis

- Complete recovery in ≈ 50% within few weeks
- Residual LL weakness & bladder or bowel dysfunction in some patients

## Treatment

- Methylprednisolone: ↓↓ Duration & ↑↑ Outcome (Pilot studies)
- Bladder care & physiotherapy

## DIAGNOSTIC CRITERIA FOR TRANSVERSE MYELITIS

1. Bilateral (and necessarily symmetric) sensorimotor and autonomic deficit of the lower limbs
2. Deficit of lower limb function
3. Deficit of lower limb function
4. Deficit of lower limb function
5. Deficit of lower limb function

# Headache

Brain is insensitive!!

## Definition

Pain or discomfort in the area from the eyebrows back to the suboccipital region

## Etiology

### A) Primary

#### 1. Migraine

#### 2. Tension-type headache (= Stress-related, muscle contraction or ordinary headache)

- Mechanism: ?Isometric contraction of masseter, temporalis or trapezius muscles
- Mild to moderate, diffuse dull-aching related to stress & anxiety (e.g., school-related)
- Severity: No associated manifestations (nausea, vomiting, disability)
- May be: Frequent, infrequent or chronic
- Diagnosis: exclusion
- Rx: Analgesics (*Ibuprofen, acetaminophen*) for acute Rx, amitriptyline for prevention

#### 3. Trigeminal autonomic cephalalgias

### B) Secondary

1. Trauma (Head or neck) & post-traumatic (Acute or chronic)
2. Tumors
3. Vascular disorder: HTN,  $\uparrow\uparrow$  CO<sub>2</sub>,  $\downarrow\downarrow$  O<sub>2</sub>, hyperpyrexia, convulsions
4. CSF pressure (High or low)
5. Substance or its withdrawal
6. Infection
7. Epileptic seizure
8. Disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth
9. Medication-overuse
10. Psychiatric disorder

## C/P of headache in toddlers

- Irritability
- Vomiting
- Rubbing of the eyes
- Photophobia

# Migraine

## Incidence

- It is the most important & most frequent type of headache in children & adolescents (10%)
- Affects ♀ > ♂ (during adolescence)

## Etiology

- ☑ **Genetic:** +ve family history (Maternal\*) in ≈ 90%
- ☑ **Migraine triggers:** Exercises, stress, menstruation, head trauma, dehydration, foods

## Pathogenesis (Vasomotor instability)

- Aura: VC (?Serotonin release or Ca influx)
- Headache: VD

## Classification (ICHD)

### 1. Migraine without aura

### 2. Migraine with aura

- Typical aura with migraine headache
- Typical aura without headache
- Familial hemiplegic migraine
- Sporadic hemiplegic migraine
- Basilar-type migraine

#### ▪ **Hemiplegic migraine:**

Transient unilateral weakness lasting for hours-days  
May be familial (AD) or sporadic

#### ▪ **Basilar-type migraine:**

Vertigo, nystagmus, ataxia, tinnitus, diplopia,  
blurring of vision, occipital headache

### 3. Childhood periodic syndromes that are commonly precursors of migraine

- Cyclic vomiting
- Abdominal migraine
- Benign paroxysmal vertigo of childhood

### 4. Retinal migraine

### 5. Complications of migraine

- Chronic migraine
- Status migrainosus: Migraine lasting > 72 hours
- Persistent aura without infarction
- Migrainous infarction

### 6. Probable migraine

## Clinical Picture

	Migraine without aura	Migraine with an aura
<b>Incidence</b>	85%	15%
<b>Aura</b>	Absent	<ul style="list-style-type: none"> <li>▪ <b>Duration:</b> &gt; 5 min but &lt; 60 min</li> <li>▪ <b>Visual</b> (Blurring, flashes of light...)</li> <li>▪ <b>Sensory</b> (Numbness &amp; parasthesia)</li> <li>▪ <b>Dysphasic</b> (Difficult verbal response)</li> <li>▪ <b>Other forms of aura:</b> <ul style="list-style-type: none"> <li>➤ Hemiplegia: True weakness</li> <li>➤ Basilar-type: Vertigo</li> <li>➤ Distortion: Alice in Wonderland</li> </ul> </li> </ul>
<b>ICHD criteria for diagnosis</b>	<ol style="list-style-type: none"> <li>1. At least 5 attacks (Fulfilling 2-4)</li> <li>2. Duration: 4-72</li> <li>3. Character: Unilateral, pulsating, moderate to severe, interfering with activity</li> <li>4. Nausea, vomiting, photophobia, phonophobia</li> <li>5. No other explanation</li> </ol>	<ol style="list-style-type: none"> <li>1. At least 2 attacks (Fulfilling 2-4)</li> <li>2. Aura (V, S, D)</li> <li>3. Visual symptoms</li> <li>4. Headache as before</li> <li>5. No other explanation</li> </ol>
<b>Headache</b>	Duration: 4-72 hrs Throbbing (Pulsating) Classically unilateral (more commonly bilaterally) Interferes with physical activities Associated symptoms: Nausea & vomiting Photophobia, phonophobia, osmophobia, cutaneous allodynia Relief with sleep	

## Childhood periodic syndromes (Migraine without headache)

### 1. Cyclic vomiting

- Recurrent attacks of vomiting
- May lead to dehydration & electrolyte disturbances
- Rx: Migraine-specific therapy
- DD: GIT (Intestinal obstruction, peptic ulcer), CNS (Tumors)  
Metabolic: Protein (OTC deficiency), CHO (HFI), FA (MCAD), Organic acidemia

### 2. Abdominal migraine

- Recurrent attacks of abdominal pain (4-72 hours)
- Usually associated with nausea, vomiting, anorexia or pallor

## Indications of Imaging in headache

1. Abnormal neurological examination
2. Abnormal or focal neurologic signs or symptoms developing during headache
3. Seizures or very brief aura (< 5 min)
4. Early morning headache
5. Headache awakens child from sleep
6. Headache with ↑↑ frequency or severity
7. Trigeminal autonomic cephalalgias (*Including cluster headache*)
8. Children < 6 yrs (or any child not able to describe headache)
9. No family history of migraine

## Treatment

### A) Acute attack

- **Analgesics:** acetaminophen, ibuprofen (10-15 mg/Kg/dose), naproxen
- **Triptan:** Almotriptan, Naratriptan, Rizatriptan, Zolmitriptan, Sumatriptan (*Imigran*)
- Sumatriptan (selective serotonin agonist): Oral, SC, nasal (*Imigran*)
- Antiemetic: Metoclopramide (*primperan*) [Mechanism: Dopamine antagonists]
- Quiet, dark room
- Sleep is an ideal Rx
- Hydration (sports drink)

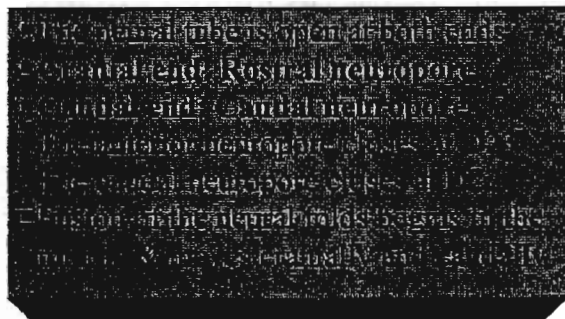
### B) Preventive therapy

- **Indications:** Frequent headache ( $\geq 1/\text{wk}$ ), disabling (missing school)
- **Duration:** 4-6 months then weaning over weeks
- **Medications**
  - Flunarizine (Ca channel blocker)
  - Amitriptyline (*Antidepressant*)
  - Propranolol ( $\beta$ -blocker): 10mg/8 hrs
  - Anticonvulsives: Na valproate, topiramate, Gapapentin, Levetiracetam
  - Cyproheptadine (*Antihistamine*)

### C) Behavioral therapy

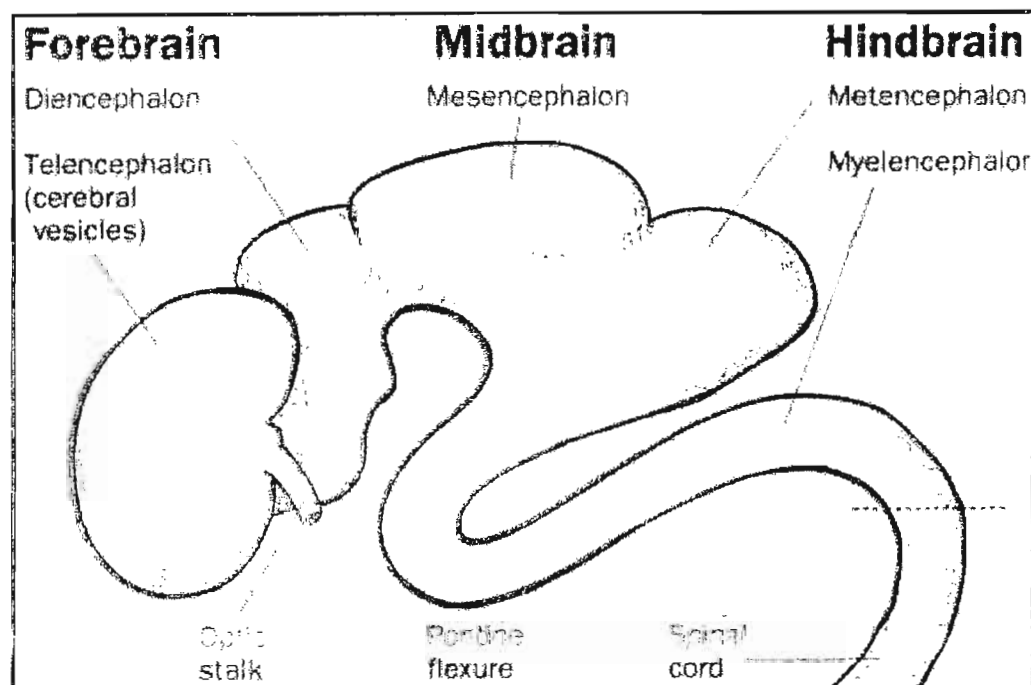
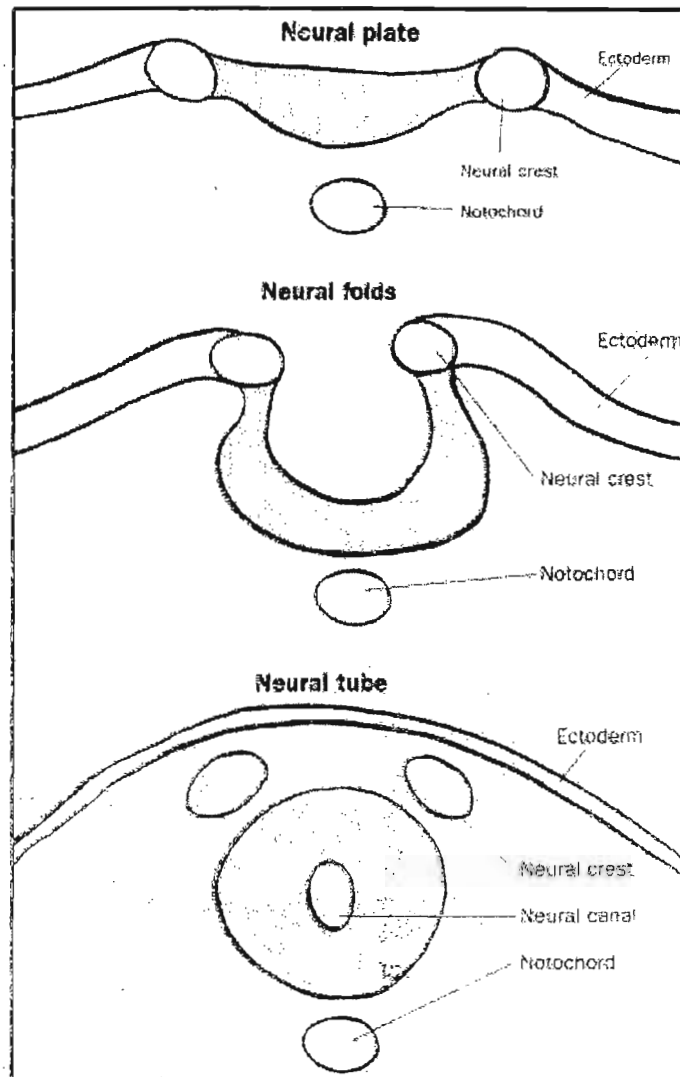
- Elimination of Rx barriers
- Avoid triggering factors
- Adequate sleep on regular basis
- Biofeedback & self-hypnosis

# Congenital Anomalies of the CNS



## Neural tube defects:

- Spina bifida occulta
- Meningocele
- Meningomyelocele
- Encephalocele
- Anencephaly
- Dermal sinus
- Tethered cord
- Syringomyelia
- Diastomatomyelia
- Lipoma involving the conus



# Neural Tube Defects

## Definition

- Failure of closure of the neural tube (Between 3<sup>rd</sup>-4<sup>th</sup> weeks IU-life)

## Etiology

- Drugs (Valproate), Chemicals
- Maternal malnutrition, obesity, DM, hyperthermia
- Genetic: Mutation in folate-responsive enzyme pathway
- Maternal **periconceptional** folate use reduces the risk of NTD by > 50 % (Mechanism?)

## Prenatal Diagnosis

- Alpha-fetoprotein (AFP) and acetylcholinesterase in the amniotic fluid and maternal blood

# Spina Bifida Occulta

(Occult spinal dysraphism)

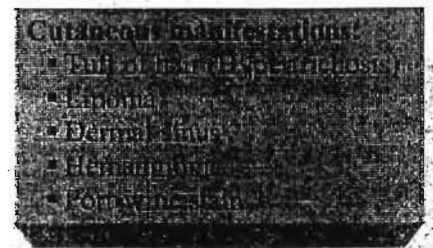
## Definition

- Midline bone defect due to failure of union of the laminae (No protrusion of meninges)
- Usually involves L5 & S1

**Incidence** 10% of live births

## Clinical Picture

- Most patients are asymptomatic
- Cutaneous manifestations: may be present
- Association: syringomyelia, tethered cord, diastematomyelia...
- Dermal sinus: recurrent meningitis, why?



## Investigations

- X-ray spine, MRI spine

# Meningocele

## Definition

- Defect of the vertebral column (Spina bifida) with protrusion of the meninges (normal cord)

## Clinical Picture

- Midline fluctuant mass (+Ve Transillumination)
- Covered with skin (may be thin)
- Neurologic, urologic & orthopedic examination is mandatory
- Association: syringomyelia, tethered cord, diastematomyelia

## Investigations

- X-ray spine, MRI spine
- Abdominal US & VCUG
- CT brain, why?

## Treatment Surgery

- **Immediate:** Leaking CSF, thin skin
- Can be **delayed:** Full-thickness skin, normal neurologic findings



# Myelomeningocele

### Definition

- Defect of the vertebral column (Spina bifida) with protrusion of the meninges & spinal cord
- Site: **lumbosacral area** (75%)

**Incidence** 1:4.000 live birth (**RR**: 4% after 1<sup>st</sup> affected baby, 10% after the 2<sup>nd</sup> one)

### Clinical Picture

- Midline saclike structure covered with thin membrane (No skin), usually **lumbosacral**
- CSF leak is common
- Neurologic, urologic & orthopedic examination is mandatory
- Flaccid paraplegia (LMNL), ↑↑ incidence of LL deformities (clubfoot, contractures)
- 80% have hydrocephalus
- **Cervical or upper thoracic** myelomeningocele: minimal neurologic deficit
- **Low-sacral** myelomeningocele: bowel & bladder dysfunction but no motor affection

### Investigations

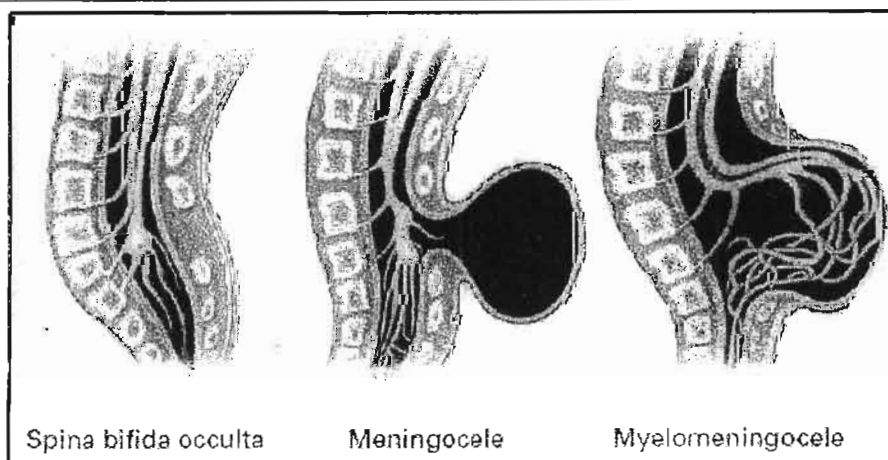
#### Prevention

- All females: Folic acid 0.4 mg daily
- High-risk females (previously affected child): Folic acid 4 mg daily
- Supplementation should be started 1 month before planned conception
- Avoid trimethoprim, why?
- Avoid anticonvulsive drugs: valproic acid, phenytoin, phenobarbitone, carbamazepine

#### Treatment

- Surgical repair with days (Immediate if there is CSF leak)
- VP shunt
- Orthopedic Rx (Deformities)
- Urinary: CIC, why?

	Spina bifida occulta	Meningocele	Meningomyelocele
<b>Herniation</b>	None	Meninges	Meninges & Spinal cord
<b>Coverings</b>	Skin	Skin ( <i>may be thin</i> )	Thin membrane (No skin)
<b>C/P</b>	- Asymptomatic - Lipoma, tuft of hair, sinus	Fluctuant midline mass	- Paraplegia - Sphincteric disturbances
<b>Investigation</b>	Plain X-ray	- Plain X-ray & MRI spine, CT brain - Abdominal US & VCUG	
<b>Treatment</b>	Reassurance	Surgery	



# Spinal Cord Disorders

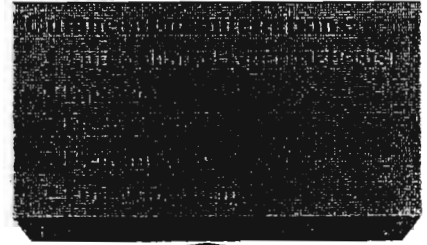
## Tethered Cord

### Definition

- ☒ **Normally**, spinal cord ends by the conus medullaris at L1
- ☒ **Tethered cord**: Fixation of the spinal cord with restricted movement (Regardless the cause)
- ☒ **Tethered cord syndrome**: Neurological symptoms due to spinal cord fixation

### Etiology

1. Thickening of filum terminale
2. Occult dysraphism: e.g., diastematomyelia
3. Repair of an open meningocele
4. Surgery disrupting spinal cord pia matter



### Clinical Picture

- At birth: open meningocele, occult dysraphism
- Neuro-orthopedic syndrome: Asymmetry of feet, calf muscle atrophy, absent ankle reflex
- UB dysfunction (incontinence), motor weakness, sensory manifestation, severe back pain

### Investigations

- MRI
- Renal US, urodynamics

### Treatment

- Surgical repair (Good in thickened filum terminale but may show recurrence in other causes)

## Syringomyelia

### Definition

- ☒ Cystic distension of the spinal cord caused by obstruction of flow of spinal fluid
- ☒ Three forms:
  - Communicating syringomyelia: Ventricular CSF communicates with spinal CSF
  - Non-communicating syringomyelia: 2ry to intramedullary tumors or obstructive lesions
  - Post-traumatic syringomyelia

### Clinical Picture

- Insidious onset & slow progression (Years)
- Central cord syndrome: UL numbness, weakness, trophic changes (Why UL?)
- Progressive scoliosis
- UB dysfunction (incontinence), motor weakness (spastic paraplegia)
- No pain except in...
- Association with Chiari malformation is frequent

### Investigations MRI

### Treatment

- Rx of the cause
- Syrinx-to-subarachnoid shunt



## Channelopathies & related disorders

	Inheritance	Gene	C/P
<b>Cl Channelopathies</b>			
Myotonia congenita (Thomsen)	AD	7q (CLC1)	Myotonia
<b>Na Channelopathies</b>			
Paramyotonia congenital	AD	17q (SCNA4A)	Paramyotonia
Hyperkalemic periodic paralysis	AD	17q (SCNA4A)	Periodic paralysis
Hypokalemic periodic paralysis	AD	17q (SCNA4A)	
<b>K Channelopathies</b>			
Myotonia fluctuans	AD	17q (SCNA4A)	Myotonia
Myotonia permanens			
Acetazolamide-responsive myotonia			
<b>Ca Channelopathies</b>			
Hypokalemic periodic paralysis	AD	1q (Dihydropyridine receptor)	Periodic paralysis
Myotonic chondrodystrophy (= Schwartz-Jampel disease)	AR	1q (Perlecan)	Myotonia
Malignant hyperthermia	AD	19q (Ryanodine receptor)	Anesthesia...

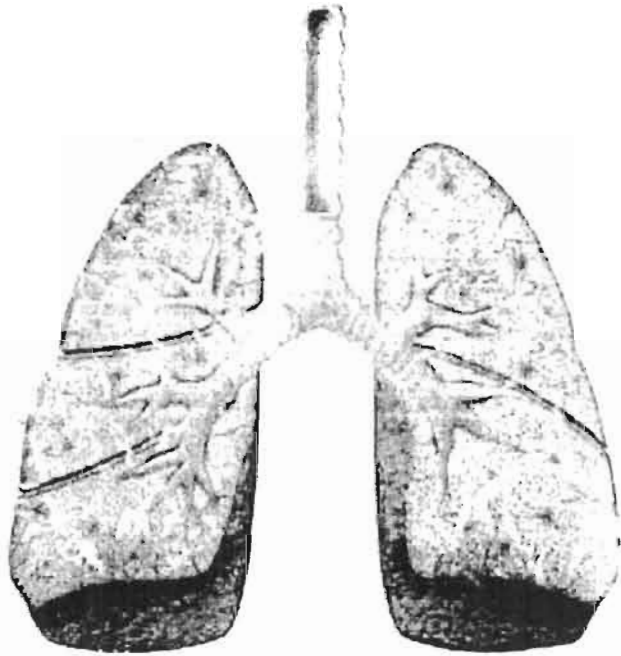
## Disorders of Neuronal Migration

### Introduction

- Neurones do not & cannot migrate "Misnomer"
- Migration of **neuroblast** during development is mainly centrifugal
- **Heterotopia**: Cells displaced within their organ (Neurones displaced in the white matter)
- **Ectopia**: Cells displaced outside their organ (Neurones in the leptomeninges)
- Disorders of migration have variable severity
- Diagnosis: Brain MRI
- Types

	Pathology
<b>Lissencephaly</b>	Absence of cerebral convolutions
<b>Schizencephaly</b>	Unilateral or bilateral clefts within the cerebral hemispheres
<b>Neuronal Heterotopia</b>	Periventricular or Subcortical
<b>Polymicrogyrias</b>	Too many small gyri (Wrinkled)
<b>Pachygyria</b>	Broad wide gyri
<b>Porencephaly</b>	Cyst or cavity within the brain Pseudo-porencephalic cyst: Acquired





# **Pediatric Pulmonology**

By

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**2013**

# Chest Examination

## A) Inspection

1. Shape: Pigeon, Barrel-shaped, Pectus excavatum
2. Symmetry:
3. Respiratory movements
  - Rate
  - Working ala nasi, retraction, grunting
  - Work of breathing: Accessory muscles of respiration
  - Paradoxical chest wall movements

### Symmetry:

- ☒ Unilateral bulge
  - Effusion, Pneumothorax
- ☒ Unilateral retraction
  - Collapse, Fibrosis

How to DD? Resp. movements

	Heart Rate (min)	Respiratory Rate (min)	Blood Pressure
Newborn	100-150	60	80 / 50
6 months	120	50	80 / 60
1-5 year	120	40	90 / 60
5-8 years	100	30	100 / 70
10 years	90	20	100 / 70
≥ 12 years	90	12-18	110 / 70

## B) Palpation

1. Mediastinal position
  - Heart
  - Trachea
2. Chest expansion
3. TVF

TVE/VR	Pathology
↑↑	Consolidation
↓↓	Effusion/Collapse

## C) Percussion

- Limited value in small infants

Note	Pathology
Resonant	Normal
Hyperresonant	Emphysema, Pneumothorax
Dull	Consolidation, Collapse
Stony dull	Effusion

## D) Auscultation

- **Breath sounds:** Vesicular, Harsh vesicular, Bronchial
- **Adventitious sounds:** Wheezes, Crepitations, Rub
- Conducted upper airway sounds are the most common cause of false +ve chest findings
- D'Espine sign: Bronchial breathing below T4 vertebra (T2 spine) Cause: Mediastinal LN

### Non-pulmonary causes of clubbing:

- **Cardiac:** Cyanotic CHD, IE
- **Pulmonary:** Chronic hypoxia
- **Hematologic:** Thalassemia
- **GIT:** IBD (UC, CD), small bowel lymphoma, polyposis coli, liver cirrhosis
- **Unilateral clubbing:**
  - Vascular disorders (Subclavian arterial aneurysm, brachial AVF)
  - Median nerve injury
  - Shoulder subluxation
  - Local trauma

**E) Invasive:****☒ Endoscopy**

- Laryngoscopy: Direct & indirect
- Bronchoscopy:
  - Diagnostic: Recurrent pneumonia, suspected FB, hemoptysis
  - Therapeutic: Removal of FB & Bronchoalveolar lavage (BAL)

**☒ Thoracoscopy****☒ Lung biopsy:** Open or transbronchial**☒ LN biopsy****☒ Thoacocentesis:** Obtaining fluid from the pleural cavity

Needle puncture should be along the upper border of the rib, why?

Complications: Infection, bleeding, pneumothorax, liver/spleen injury

**Pleural fluid examination** (Physical, Chemical, Cytological & Bacteriological)

- Physical: Clear in transudate, turbid in others
- Cytological: ↑↑ PNLs (Exudate), ↑↑ Lymphocytes (TB), Malignant cells
- Chemical: Milky fluid with ↑↑ TAG (Chylous), blood-stained (Tumors)
- Bacteriological: Culture

	<b>Transudate</b>	<b>Exudate</b>
<b>Aspect</b>	Clear	Turbid
<b>Specific gravity</b>	Low (< 1015)	High (> 1015)
<b>Proteins</b>	Low (< 2.5 g/dl)	High (> 2.5 g/dl )
<b>Cell Number</b>	Few (< 2000 /mm <sup>3</sup> )	Many (> 2000 /mm <sup>3</sup> )
<b>Cell Type</b>	Lymphocytes	PNLs
<b>LDH</b>	Low (< 200 IU/L)	High (> 200 IU/L )

# Investigations of Chest Diseases

## A) Laboratory

### ☒ Blood

- **CBC:** Hb (anemia of chronic disease), **WBC** (↑↑ in infection, ↓↓ in immunodeficiency) & **PLT** (Collagen-vascular diseases)
- **ESR & CRP:** ↑↑ Chest infection (TB)
- **Arterial blood gases (ABG)**
- **ANCA** (Anti-neutrophil cytoplasmic Ab): Wegener granulomatosis & Churge-Strauss
- **Anti-centromere Ab:** in scleroderma

### ☒ Sweat chloride test: Cystic fibrosis

### ☒ Microbiology

- **Sample:** Sputum, ETT, stomach wash, fasting gastric aspirate, BAL or lung biopsy
- **Examination**
  - Cytological: ↑↑ PNLs (Bacterial), ↑↑ Lymphocytes (TB & viral), Malignant cells  
Hemosiderin granules in macrophages (Hemosiderosis)  
Lipid laden macrophages in aspiration pneumonia  
Direct smear for bacteria & fungi
  - Culture

### ☒ Urine

- **Urinalysis & Urinary protein/creatinine ratio** ( $N < 0.2$ ): Proteinuria, when?
- **Urine culture & sensitivity**

## B) Imaging

### ☒ CXR (PA & Lateral views):

- **Lung:** Pulmonary congestion & infection
- **Heart:** Cardiomegaly

### ☒ Upper airway films

- **Steeple sign:** Subglottic tracheal narrowing (Inverted V appearance)
- **Thumb sign:** Epiglottitis

### ☒ CT & MRI: Mediastinal lesions, bronchiectasis & cystic parenchymal diseases

### ☒ Fluoroscöpy

### ☒ Sinus: X-rays & CT

### ☒ Chest transillumination: Infants < 6 months (*pneumothorax*)

### ☒ Barium swallow

### ☒ Bronchography: Bronchiectasis

### ☒ Angiography; Vascular ring

### ☒ Radionuclide Lung scan (Isotopic scan)

- Assessment of ventilation & perfusion
- Diagnosis of pulmonary embolism & congenital vascular anomalies

## C) Pulmonary function tests

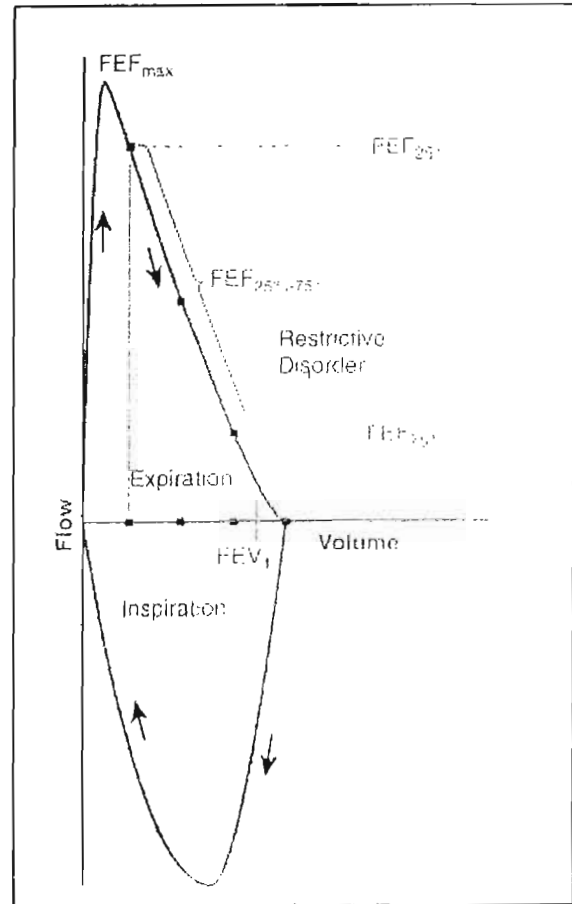
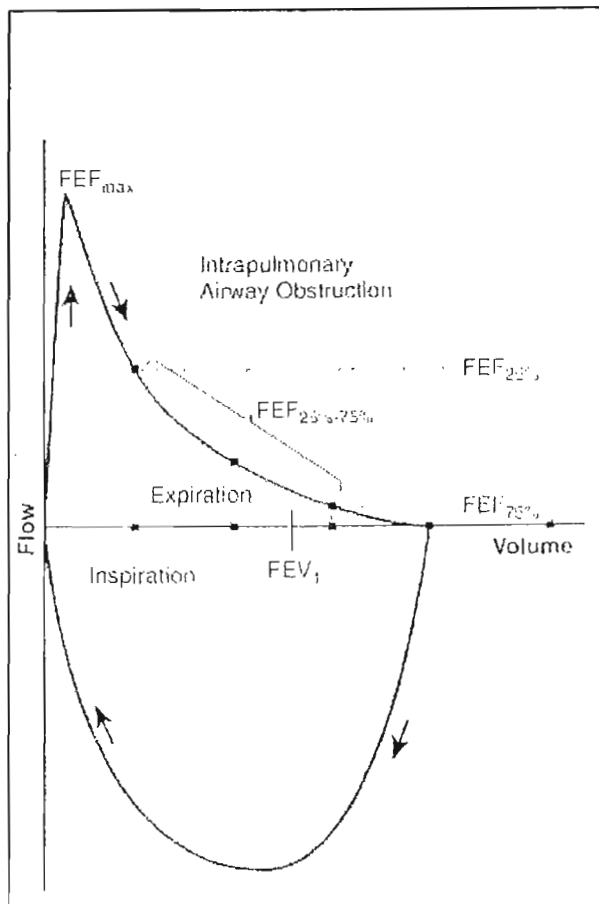
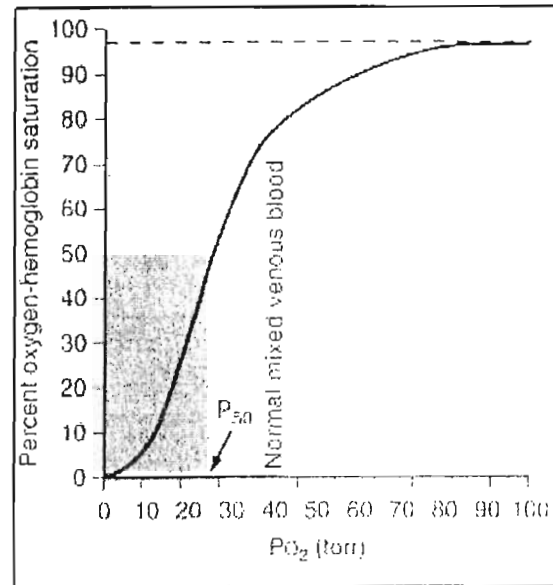
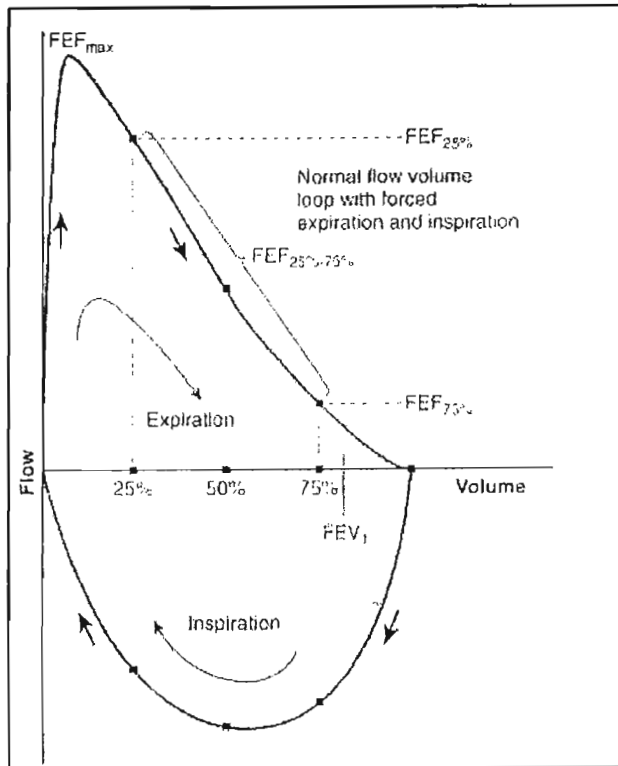
- ☒ **Spirometry:** measurement of VC and its subdivisions and expiratory flow rates
- ☒ **Plethysmography:** measurement of TLC, Airway resistance
- ☒ **Diffusing capacity for carbon monoxide (DLCO):** measurement of diffusion
- ☒ **Exercise testing**

## D) Polysomnography

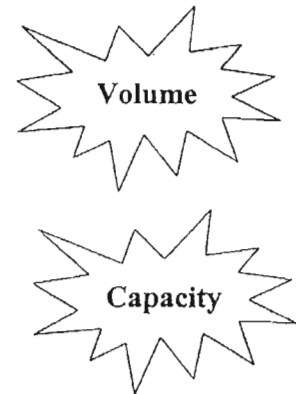
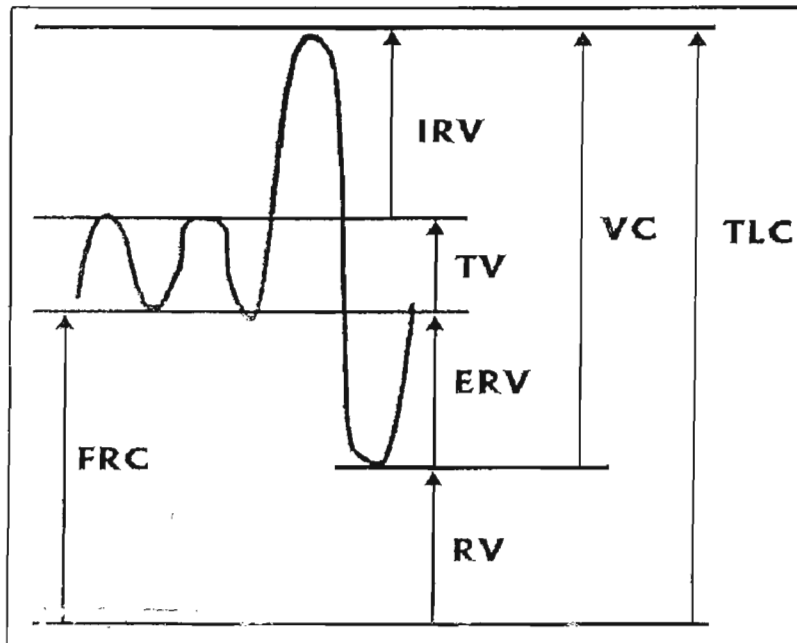
- It is the gold standard test for obstructive sleep apnea or hypoventilation
- pH probe studies can be added (GERD)



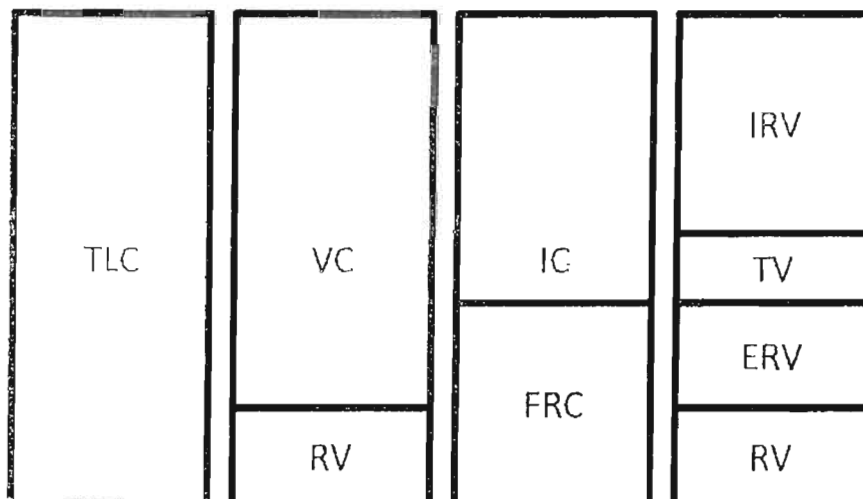
# Flow Volume Loops



# Lung Volumes & Capacities



Volume/ Capacity	Definition
Tidal volume	Volume of air inspired or expired in a single breath at rest
Inspiratory reserve volume (IRV)	Maximum gas volume that can be inhaled following normal inspiration
Inspiratory capacity (IC)	Amount of air inspired by maximum inspiration after normal expiration
Expiratory reserve volume (ERV)	Maximum gas volume that can be exhaled following normal expiration
Residual volume (RV)	The volume of gas remaining in the lungs after maximum expiration
Vital capacity (VC)	Maximum volume that can be exhaled following maximal inspiration
Functional residual capacity (FRC)	Volume of air remaining in the lung following normal quiet expiration
Total lung capacity (TLC)	Maximum volume of air present in the lungs after maximum inspiration



## **Causes of Recurrent or Persistent; Cough in Children**


### 1. Asthma

- Aspiration
- Alpha-1-Antitrypsin deficiency
- Aspergillosis

### 2. Bronchitis

- Bronchiolitis
- Bronchiolitis obliterans
- Bronchopneumonia
- Bronchopulmonary dysplasia
- Bronchiectasis
- Pneumonitis
- Pertussis
- Poisoning (Organophosphorous)
- Post-nasal discharge (Sinusitis)

### 3. Cystic fibrosis

- Ciliary dyskinesia
- Cardiac (Heart failure)
- Cricocricoid in coordination
- Cacinoid syndrome
- Chronic renal failure
- Compression 

#### **Compression:**

- **Lumen:** FB, secretion, tumors
- **Wall:** Ttracheomalacia, bronchomalacia, tumors
- **Outside:** LN, cysts, vascular ring, tumors

### 4. Endobronchial (TB & tumors)

- Esophageal atresia (TOF)

### 5. Foreign body inhalation

- Fungal infection

### 6. GERD

### 7. Heart failure

- Hiatus hernia
- Hemosiderosis
- H-shaped tracheo-esophageal fistula
- Habit cough (Psychogenic cough)

### 8. Immunodeficiency

- Immotile cilia syndrome
- Irritation: Smoking
- Irritation of the external auditory canal

## Causes of Cough

### A) Acute cough (Duration < 2 wks)

- a. **With RD:** Acute bronchiolitis, Acute asthmatic attack, Pneumonia
- b. **Without RD:** Acute bronchitis, Acute laryngitis, Acute sinusitis

### B) Prolonged cough (2 wks - 2 months)

- a. Complicated bronchitis (Bacterial bronchitis, pneumonia, segmental collapse)
- b. Acute sinusitis
- c. Pertussis & pertussis-like illness

### C) Chronic cough (Duration > 2 months)

- Chronic infections: TB, bronchiectasis
- Immunodeficiency
- FB inhalation
- Persistent asthma
- Recurrent aspiration: GERD, TOF
- Congenital abnormality of lung and heart
- Cystic fibrosis
- Bronchopulmonary dysplasia

## Diagnostic Approach for Cough

### A) History

- ☒ Character of cough
- ☒ History suggestive of FB inhalation: **Sudden** onset of cough, choking & cyanosis
- ☒ Recurrence & seasonal variation: Asthma
- ☒ TB toxemia: Night fever, night sweating, loss of weight, loss of appetite
- ☒ Aspiration
- ☒ Smoking & passive smoking
- ☒ Nasal obstruction & nasal discharge
- ☒ Other systems: GIT symptoms (CF), Cardiac (HF)
- ☒ Animal exposure: Chlamydia (birds), Yersinia (rodents), Q fever (cattle & sheep)



Character	Diagnosis
Productive	Bronchitis, bronchiectasis
Brassy (Metallic)	Tracheitis
Bovine (Barking)	Acute laryngitis
Tight (Wheezy)	Asthma (Reactive airways)
Nocturnal	Asthma, sinusitis
Early morning	Asthma & bronchiectasis
With vigorous exercise	Asthma (exercise-induced)
Disappears with sleep	Habit cough
Paroxysmal	Pertussis
Staccato	Chlamydia pneumonia

### B) Examination

#### a. General

- Pallor: anemia (anemia of chronic disease or hemosiderosis)
- Failure to thrive, clubbing & cyanosis

#### b. Chest examination

- Inspection, palpation, percussion & auscultation

### C) Investigations: See before

# **Bronchial Asthma**

## **Definition**

- Chronic diffuse **inflammatory** obstructive disorder of the airways characterized by
  - Airway hyper responsiveness (AHR)
  - High degree of reversibility either spontaneously or with treatment
- Bronchial asthma is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
- The majority of asthmatic children have allergic component
- Asthma can be effectively controlled, although it cannot be **cured**

## **Epidemiology**

Prevalence of BA is ↑↑

- 10% of school children
- 80-90% of asthmatics are symptomatic before the age of 6 yrs
- Of all young children with recurrent wheezes, only a minority will have persistent asthma
- Children living in rural areas & farming communities are less likely to develop asthma and allergy (**Hygiene theory**)
- Risk for development of **persistent asthma**:
 

<ul style="list-style-type: none"> <li>○ Parental asthma</li> <li>○ Tobacco exposure</li> <li>○ Wheezes without cold</li> <li>○ Allergy</li> <li>(atopic dermatitis, allergic rhinitis, food allergy)</li> </ul>	<ul style="list-style-type: none"> <li>○ Male sex</li> <li>○ Low birth weight</li> <li>○ Reduced lung function at birth</li> <li>○ Chlorinated swimming pools</li> <li>○ Use of paracetamol</li> </ul>
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## **Etiology** (Multifactorial)

- Environmental exposure (Asthma triggers)
- Genetic: Multiple genes causing asthma & asthma-related traits (atopy, atopic dermatitis...)

## **Patterns of recurrent wheezing in childhood** (Clinical pattern)

### **A) Transient early wheezing**

- Recurrent wheezes triggered by viral infection
- Preschool years & resolves by 5 years of age
- No asthma later in life

### **B) Persistent atopy-associated asthma**

- IgE-mediated
- Associated with atopy; atopic dermatitis, allergic rhinitis, food allergy
- Highest risk for persistent asthma

### **C) Non-atopic wheezing**

- Recurrent wheezes triggered by RSV
- Resolves in late childhood
- No increased risk for persistent asthma

### **D) Late-onset asthma in females associated with obesity & early-onset puberty**

- Onset: 8-13 yrs

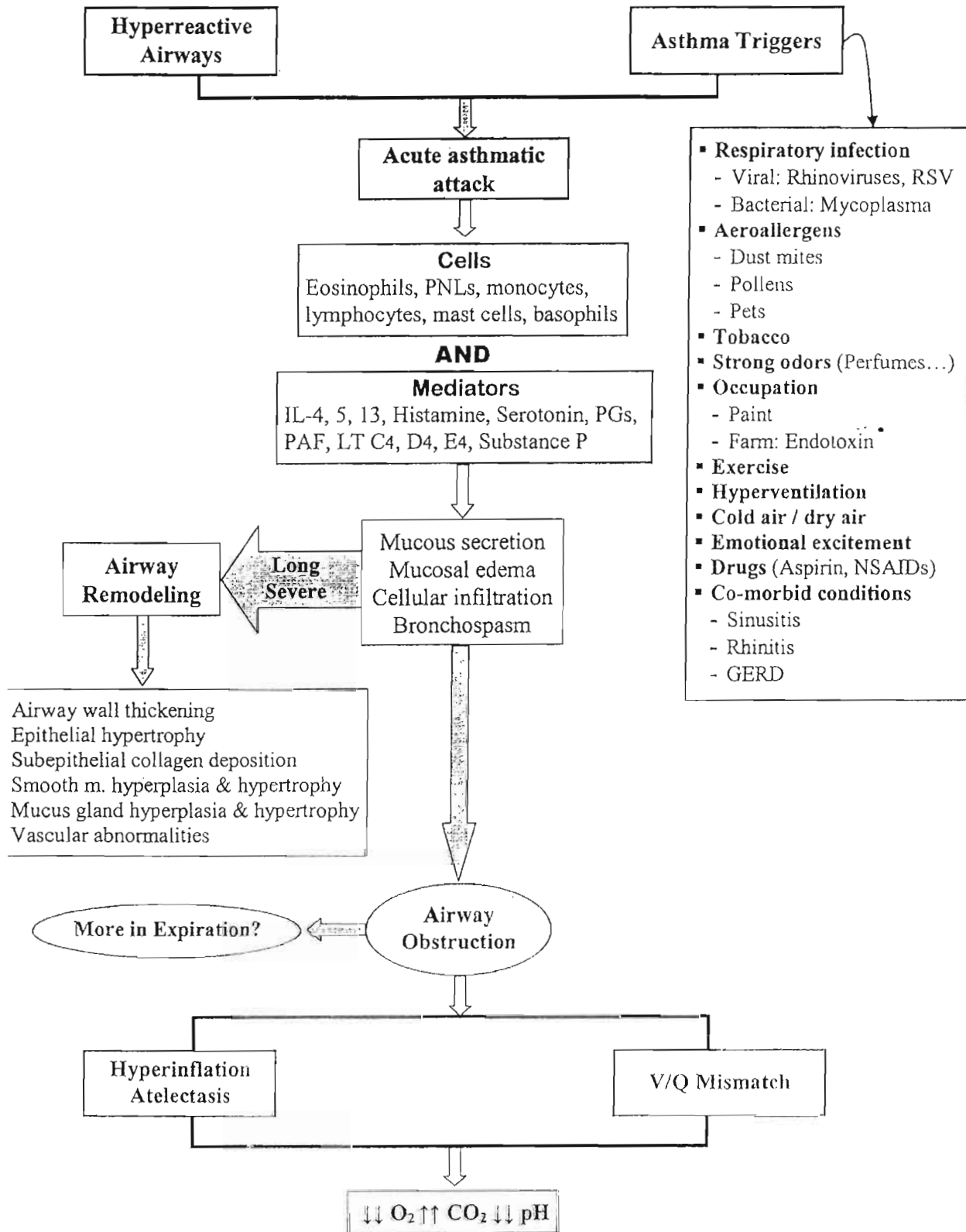
### **E) Asthma with declining lung function**

- Male gender
- Progressive airflow limitation

### **F) Occupational-type asthma**

- Farms: Endotoxin exposure

## Pathogenesis



**Clinical Picture** (*It is a clinical diagnosis*)

Markers of atopy

**A) Symptoms**

- **Recurrent**, intermittent dry **cough** (Nocturnal &/or early morning)
- **Cough or wheezes after exercise**
- **Cough or wheezes after exposure to airborne allergens**
- **Atopic March**: Infants with atopic dermatitis → Allergic rhinitis → Asthma
- Co-morbid conditions: can mimic or worsen asthma

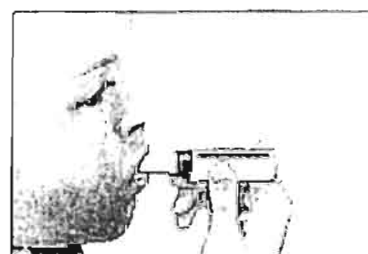
Atopic March

**B) Signs**

- Vesicular breath sounds with prolonged expiration
- Expiratory **wheezes** (Usually sibilant)
- Variable degrees of **RD** (Tripod position) →
- Chest Ex.: with prolonged expiration, expiratory wheezes.
- Severity of asthma attacks: Mild, Moderate or Severe



	Mild	Moderate	Severe	Imminent respiratory arrest
<b>Breathlessness</b>	Walking	Rest	Rest	
<b>Talking</b>	Sentences	Phrases	Words	
<b>Alertness</b>	Agitated	Agitated	Agitated	Drowsy
•				
<b>RR</b>	↑↑	↑↑	↑↑	
<b>Pulse</b>	< 100	100-120	> 120	Bradycardia
<b>Pulsus paradoxus</b>	Absent	May be present	Usually present	Absent
<b>Accessory muscles</b>	No	Yes	Yes	Paradoxical
<b>Wheezes</b>	Yes	Yes	Yes	Absent
<b>PEF</b>	> 70%	40-70%	< 40%	< 25%
<b>PaO<sub>2</sub></b>	Normal	> 60 mmHg	< 60 mmHg	
<b>PaCO<sub>2</sub></b>	< 42 mmHg	< 42 mmHg	> 42 mmHg	
<b>SaO<sub>2</sub></b>	> 95%	90-95%	< 90%	

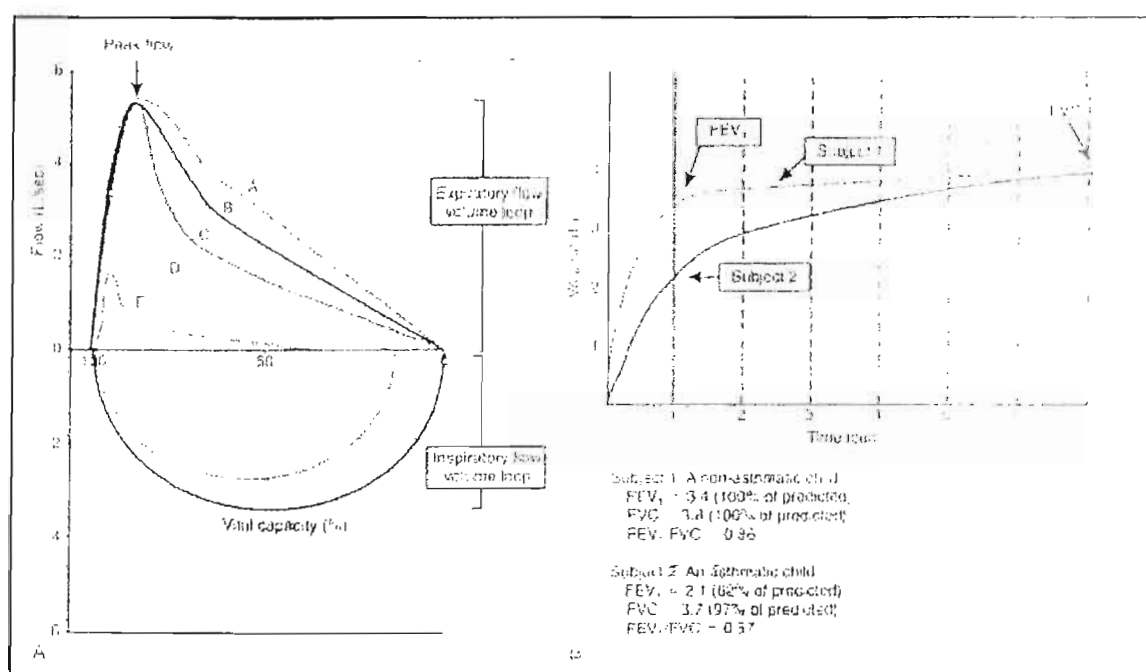


## Investigations

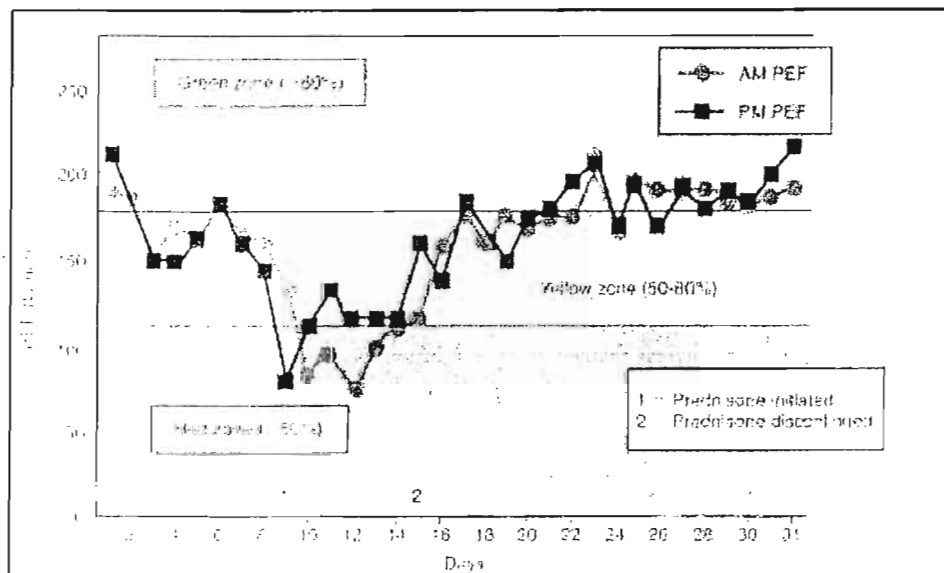
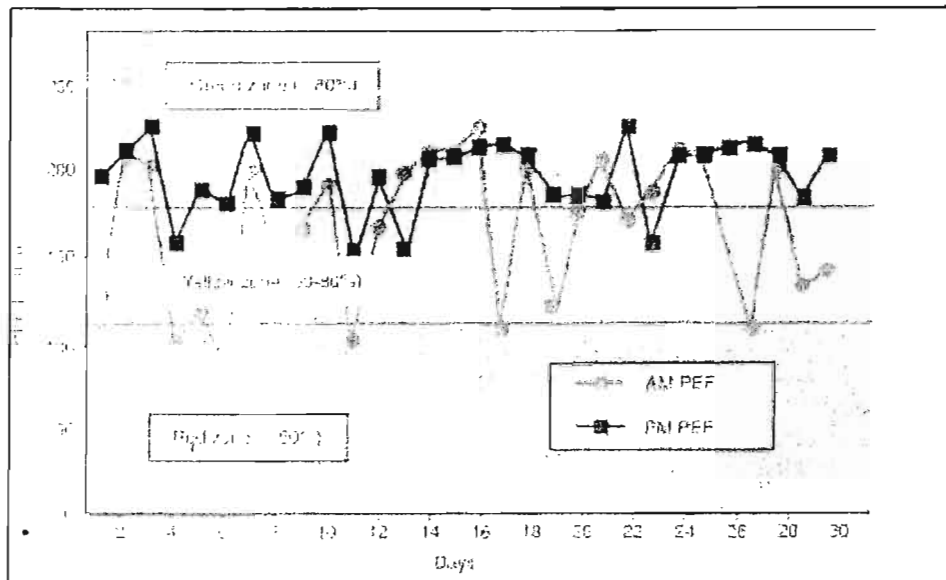
- CBC ( $\uparrow\uparrow$  Eosinophils)
- $\uparrow\uparrow$  Serum IgE (Total & specific)
- ABG
- Prick skin test
- Inhalation bronchial challenge (*Methacholine or histamine*)
- Exercise challenge (*Running for 6-8 minutes*)
- FENO: Exhaled NO "Marker of airway inflammation"
- CXR: Hyperinflation
- Pulmonary function tests (**Spirometry**): *Feasible in children > 6 yrs*
  - FEV<sub>1</sub>:  $\downarrow\downarrow$
  - FEV<sub>1</sub>/FVC:  $\downarrow\downarrow < 80\%$
  - Bronchodilator response to inhaled  $\beta_2$  agonists:  $\uparrow\uparrow$  FEV<sub>1</sub>  $\geq 12\%$
  - Exercise challenge:  $\downarrow\downarrow$  FEV<sub>1</sub>  $\geq 15\%$
  - Variation in FEV<sub>1</sub> or PEF  $\geq 20\%$
  - PEF (**Daily**): 3 zones (Green "80-100%", Yellow "50-80%" & Red "<50%")

Parameter	Obstructive	Restrictive
FVC	Normal or Decreased	Decreased
FEV <sub>1</sub>	Decreased	Decreased
FEV <sub>1</sub> /FVC	Decreased	Normal (or Increased)
FEF <sub>25-75</sub>	Decreased	Normal
TLC	Normal or Increased	Decreased
RV	Increased	Normal or Decreased
RV/TLC	Increased	Normal or Decreased

**FEV<sub>1</sub>**: Forced expiratory volume in the 1<sup>st</sup> sec.  
**FVC**: Forced vital capacity

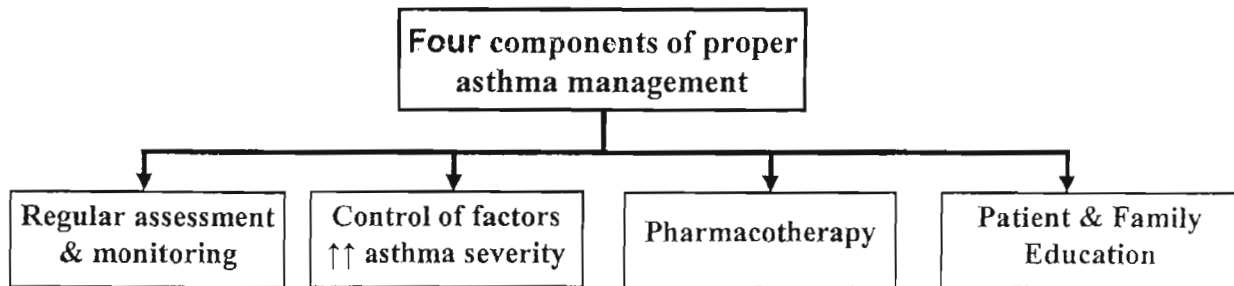






# Treatment of Bronchial Asthma

(National Asthma Education & Prevention Program)



## A) Regular assessment & monitoring

- Assessment of asthma severity: Mild or persistent (Mild, moderate, severe)
- Assessment of asthma control: Well-controlled, not well-controlled, very poorly controlled
- Responsiveness to therapy (& medications side effects)
- Check-up: 2-4 / year are recommended (Items to be checked??)
- Spirometry is recommended at least annually
- PEF is recommended daily (preferably in the morning)

## B) Control of factors ↑↑ severity of asthma

Egg-allergy!

- ↓↓ Environmental exposure (e.g., annual Influenza vaccine...)
- Rx of co-morbid conditions (GERD, Rhinitis, Sinusitis)
  - a. GERD
    - Occurs in 60% of asthmatic patients
    - Mechanism: Aspiration & vagal stimulation
    - Investigation:
    - TTT: Positioning, dietary management, Drugs (Antacids & H<sub>2</sub> blockers, proton-pump inhibitors) & rarely surgical management
  - b. Rhinitis
    - Occurs in 90% of asthmatic patients
    - TTT: Avoidance of offending allergens, oral antihistaminics, nasal steroids
  - c. Sinusitis
    - Occurs in 60% of asthmatic patients
    - TTT: Antibiotics, nasal saline irrigation, nasal steroids

## C) Pharmacotherapy

- Quick-relief, controller therapy & stepwise approach
- Rx of asthma exacerbation

## D) Patient & family education

- Basic facts about asthma
- Medications side effects
- Goals of management
- Environmental asthma triggers
- Written management plan (Daily management & Rx of exacerbations)
- Check adherence to Rx
- Regular F/U visits

# Management of Asthma Exacerbations

## Quick-relief medications

### 1. Short-acting inhaled $\beta_2$ -agonist (SABA)

#### ☒ Salbutamol

- Inhalation (100 $\mu$ g/puff): 2 puffs every 20 min
- Nebulization (5mg /ml): 0.5 ml + 2-3 ml NS every 20 min "0.15 mg/kg"
- IV: 0.2  $\mu$ g/kg/min. (max. 4  $\mu$ g/kg/min)
- Oral (Ventoline 2mg/5ml): 0.6 mg/Kg/day

#### ☒ Terbutaline, albuterol, levalbuterol

### 2. Anti-cholinergic agents

#### ☒ Ipratropium

- Inhalation (20  $\mu$ g/puff): 2 puffs every 6 hr
- Nebulization (0.5 mg /2 ml): every 6 hr

### 3. Short course of systemic steroids (Methylprednisolone, prednisone, prednisolone)

Dose: 1-2 mg/Kg/day for 3-7 days

### 4. Adrenaline (IM or SC): 0.01 mg/Kg/dose (*Can be repeated after 15-30 minutes*)

#### Side effects of SABA:

1. Tachycardia
2. Tremors
3. Hypokalemia
4. Hypoxemia, why?

## Asthma exacerbations:

- Acute episodes of worsening of symptoms
- V/Q mismatch: Hypoxemia
- Time: Usually 12 am- 8 am
- Complications: Air leak (Pneumomediastinum & pneumothorax)
- **Status asthmaticus:** Severe exacerbation **not** responding to standard Rx
- **Risk factors for asthma morbidity & mortality:**
  - o Previous asthma exacerbations
  - o  $\geq 2$  Hospitalization in the past yr
  - o Poor response to systemic steroids
  - o Male sex
  - o Low birth weight
  - o Urban environment
  - o Tobacco exposure
  - o Antigen exposure
  - o Poverty
  - o Crowding
  - o Mother < 20 yrs
  - o Inadequate medical care
  - o No regular F/U
  - o Lack of action plan
  - o Delay in care
  - o Alcohol or substance abuse

## A) Home management

- All children with asthma should have a written action plan ( $\downarrow\downarrow$  Mortality)
- Initial Rx: Inhaled SABA (3/hr)
  - Good response (= Symptoms subside + PEF > 80%):  
SABA every 4 hr + contact physician
  - Incomplete response (= Symptoms improve + PEF 50-80%):  
SABA + Oral steroids (prednisone) + Consult physician
  - Poor response (= Symptoms persist + PEF < 50%):  
SABA + Oral steroids (prednisone) + Transport to ER  
NB: Injectable form of adrenaline (Life-threatening conditions)

## B) ER management

- **History taking:** Onset, triggers, medications received, current Rx, previous attacks
- **Assessment:**
  - **Clinical:** Vital signs, mental status, breathlessness, RD(4), accessory muscles, chest expansion, air entry, wheezes, silent chest, pulsus paradoxus
  - **Laboratory:** Oxygenation (pulse oximetry, ABG), PFTs (FEV1 or PEF)
- **Risk factors for morbidity & mortality:** *See before*
- **Management:**
  - Oxygen therapy: Mask or prongs
  - Inhaled SABA (every 20 min) ± Ipratropium
  - Systemic steroids (Oral or IV)
  - IM adrenaline may be given in severe cases

## C) Hospital management

- **Indications:** Failure of response within 1-2 hrs of intensive Rx Or high risk of mortality
- **Assessment:**
  - **Clinical:**
  - **Laboratory:** Oxygenation (pulse oximetry, ABG), electrolytes, CBC, CXR
- **Management:**
  - Oxygen therapy: Mask or prongs
  - Inhaled SABA (may be continuous) ± Ipratropium
  - Systemic steroids (IV or oral)
  - IV Theophylline
  - IV  $\beta_2$ -agonist
  - IM or SC adrenaline: 0.01 mg/Kg/dose (*Can be repeated after 15-30 minutes*)
  - IV  $\text{MgSO}_4$
  - Inhaled heliox
  - Hydration status: Dehydration Vs the risk of SIADH
  - ETT & Mechanical ventilation: may be needed in cases of respiratory failure
  - Mucolytics & chest physiotherapy should be **avoided**, why?

### Mechanical ventilation in severe asthma

- Mechanical ventilation should be anticipated
- Elective intubation is safer than emergency intubation
- Careful balance of enough pressure:
  - Low pressure → Hypoventilation (airway obstruction)
  - High pressure → Hyperinflation, Air leak (Barotrauma)
- Settings:
  - ↑↑ Expiratory time (I/E = 1:3 or even 1:4)
  - ↓↓ PEEP ≤ 4 cm H<sub>2</sub>O (Zero-PEEP may be used)
- Myopathy in asthma: Hopkins syndrome, steroids, fatigue

### Discharge (*Stabilization*)

- Normal physical findings
- Oral intake
- PEF > 70%
- O<sub>2</sub> saturation > 92% (room air) for ≥ 4 hr
- Rx on discharge: Inhaled  $\beta_2$ -agonist (up to every 3-4 hrs) & steroids (for 3-7 days)
- F/U visits are planed after 1-2 wks
- Stepwise adjustment of controller Rx

**Outcome** Mortality is rare in medical centers (Most deaths occur at home)

### Prevention of asthma

- Reduce exposure to major allergens
- Avoidance of environmental tobacco smoke
- Prolonged breastfeeding
- No "solid" foods for the first 6 months
- Egg and fish only after 12 months of age
- Maternal elimination diet during breast feeding
- Avoid day-care centers during infancy
- Immunizations: All vaccines including varicella & influenza
- Hygiene theory: Microbial exposure in early life may ↓↓ asthma incidence (Rural areas)

### Prognosis

- Of all young children with recurrent wheezes, only a minority will have persistent asthma
- In children with mild asthma, the **remission** rate is ≈ 50%
- In children with severe asthma, ≈ 95% become asthmatic **adults**
- Risk for development of **persistent asthma**

## Causes of Wheezes

### Definition

Single (Non-recurrent) Wheezes	Chronic (Recurrent) Wheezes
Acute bronchiolitis	Bronchial asthma
Severe bronchopneumonia	Recurrent aspiration
FB inhalation	FB inhalation
Organo-phosphorous poisoning	Chronic infection
HF	HF
Transient bronchial hyperreactivity	Bronchopulmonary dysplasia
Asthma (1 <sup>st</sup> attack)	Bronchiolitis obliterans
	Airway compression

## Assessment of Asthma Severity

- Assign to the most severe
- Initiate higher level controller

Severity	Impairment					Risk
	Daytime symptoms	Nighttime awakening	Interference with activity	SABA use	FEV <sub>1</sub> % predicted	FEV <sub>1</sub> /FVC ratio
Mild intermittent	≤ 2/wk	≤ 2/month	No	≤ 2 d/wk	> 80%	> 80%
Mild persistent	> 2/ wk	> 2/ month	Minor	> 2 d/ wk	> 80%	> 80%
Moderate persistent	Daily	> 1/wk	Some	Daily	60-80%	75-80%
Severe persistent	Throughout the day	Frequent	Extreme	Several/d	< 60%	< 75%
						Exacerbation requiring Systemic steroids
						0-1/ yr
						≥ 2/ yr
						≥ 2/ yr
						≥ 2/ yr

**Recommended Step for initiating Rx:** Step 1, 2, 3, 4

**Age groups:** 0-4 yrs, 5-11 yrs, ≥ 12 yrs

## Classification of Asthma Control

- For patients on controller
- Assign to the most severe

Severity	Impairment					Risk
	Daytime symptoms	Nighttime awakening	Interference with activity	SABA use	FEV <sub>1</sub> % predicted	FEV <sub>1</sub> /FVC ratio
Well-controlled	≤ 2/wk	≤ 2/month	No	≤ 2 d/wk	> 80%	> 80%
Not well-controlled	> 2/ wk	> 2/ month	Some	> 2 d/ wk	60-80%	75-80%
Very poorly controlled	Throughout the day	> 1, wk	Extreme	Several/d	< 60%	< 75%
						Exacerbation requiring Systemic steroids
						0-1/ yr
						≥ 2/ yr
						≥ 2/ yr

**Well-controlled:** Keep on, consider step-down if well for ≥ 3 months

**Not Well-controlled:** Step-up, assess after 4-6 wks

**Very poorly controlled:** Short course of systemic steroids, Step up (1-2 steps) & assess in 2wks

## Stepwise Approach for Management of Asthma

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS & LABA	High-dose ICS & LABA	High-dose ICS & LABA
Alternative	-	Cromolyn or LTRA	Low-dose ICS & LTRA	Medium-dose ICS & LTRA	High-dose ICS & LTRA	High-dose ICS & Oral steroids

**Quick Relief (All patients):** Short-acting  $\beta_2$  agonists (inhaled or oral): Salbutamol, Terbutaline  $\pm$  Ipratropium ( $\pm$  Short courses of systemic steroids)  
**Stepwise approach of management:** Step down (Rx reduction) & Step up (If not controlled)



## Asthma Controller therapy

Inhaled Steroids	LABA	Leukotriene Modifiers	Other asthma controllers
<ol style="list-style-type: none"> <li>1. Beclomethasone (Becotide)</li> <li>2. Budesonide (Pulmicort)</li> <li>3. Fluticasone (Flixotide)</li> <li>4. Triamcinolone</li> <li>5. Fluticasone + Salmeterol (Seretide)</li> </ol> <p>Dose: 100<math>\mu</math>g/dose bid or tid Forms: Inhaler or Diskus</p>	<p>Salmeterol (Serevent)</p> <p>Dose: 20<math>\mu</math>g/dose bid</p>	<p>Montelukast (Singulair 5 &amp; 10 mg tab)</p> <p>Dose: 5-10 mg oral single daily dose (when?)</p>	<ul style="list-style-type: none"> <li>▪ Ketotifen (Zaditen): 0.05 mg/Kg/day bid</li> <li>▪ Cromolyn Na (Intal inhaler): 5 mg/dose qid</li> <li>▪ Sustained-release theophylline (Theo SR): 15-20 mg/kg/day bid</li> <li>▪ Oral steroids (Prednisone): 1-2 mg/Kg/day</li> <li>▪ Omalizumab (Anti-IgE)</li> </ul>



# Stridor

## Definition

It is continuous inspiratory harsh sound due to partial obstruction of the upper airways (Larynx & Trachea). Complete obstruction is fatal

## Incidence

Commoner in infants & young children, Why?

## Clinical Grading of Stridor

1. Grade I: Stridor with exertion (Crying or exercises)
2. Grade II: Stridor at rest
3. Grade III: Stridor + Retractions (Suprasternal & Supraclavicular)
4. Grade IV: Stridor + Cyanosis

## Etiology

### A) Acute Stridor

Infectious (= Croup)*	Other Causes
Acute laryngitis	Laryngeal diphtheria
Spasmodic laryngitis	Laryngeal FB
Laryngotracheobronchitis	Laryngospasm
Acute bacterial tracheitis	Laryngeal edema (Post-extubation, allergy)
Acute bacterial epiglottitis	Laryngeal compression (Retropharyngeal abscess)

### Important Remarks

- ☑ Infectious croup is much commoner
- ☑ Frequency: Viral > Bacterial
- ☑ Severity: Bacterial > Viral
- ☑ Viral: Parainfluenza, Influenza, Adenovirus, RSV
- ☑ Bacterial Causes: Tracheitis (Staphylococci), Epiglottitis (Hemophilus influenza type b)
- ☑ Laryngotracheobronchitis: Stridor is both inspiratory & expiratory

Infectious (= Croup)	Age	Etiology	Fever	Stridor
Acute laryngitis	1-3 yrs	Viral	Mild	Mild
Spasmodic laryngitis	1-3 yrs	Viral / allergic	Absent	Moderate
Laryngotracheobronchitis	1-3 yrs	Viral	Mild	Moderate
Acute bacterial tracheitis	1-3 yrs	Staph.*	High	Severe
Acute bacterial epiglottitis	3-7 yrs	Hib*	High	Severe

### B) Chronic Stridor

Congenital	Acquired
Laryngomalacia	Laryngeal stenosis (Prolonged intubation)
Tracheomalacia	Tracheal stenosis (Prolonged intubation)
Laryngeal web	Laryngeal tumors (Papilloma)
Laryngeal tumor or cyst	Laryngeal paralysis (RLN)
Laryngeal compression (Vascular ring, Goiter)	Laryngeal compression (Tumors)



## Management of Stridor

### A) Home Management

1. **Observation:** Follow-up of RD
2. **Warm moist environment:** Steamy bathroom (mist therapy)
3. **Drugs**
  - **Steroids:** Dexamethasone should be considered
  - **Antibiotics** are **not** indicated in croup, Why?

**The mainstay of Rx is the Airway Management**

**Steroids are beneficial even in mild cases**

### B) Home Management

#### Indication of hospital Rx:

- No improvement or deterioration on home treatment
- Stridor grade **III**
- Stridor grade **IV** (It is an indication of endotracheal intubation)
- Infants with grade **II**
- Suspected bacterial etiology (e.g., high fever...)

#### Components of hospital Rx:

**O<sub>2</sub> saturation < 90 % is an indication of ETT**

1. **Close observation**
  - **Clinical:** Vital signs, level of consciousness
  - **Pulse oximeter:** Continuous O<sub>2</sub> saturation monitoring
  - **ABG** may be needed
2. **Minimal disturbances**
  - Keep the child in his preferred position
  - Avoid child anxiety & crying
3. **Oxygen therapy:** *Oxygen should be humidified*
  - Oxygen mask
  - Head box (hood)
  - **Endotracheal intubation** with endotracheal tube (ETT):
    - **Indications:** Cyanosis &/or altered consciousness
    - **Precautions:** Experienced person & using smaller "than usual" ETT
  - **Tracheostomy:** if failed intubation
4. **Helium-oxygen mixture (Heliox):** in severe cases
5. **Warm moist environment:** Nebulizer (± Adrenaline)
6. **IV Fluids**
7. **Drugs**
  - **Antibiotics:** in epiglottitis Ampicillin
  - **Steroids:** Oral/IM Dexamethasone (Or Inhaled steroids; Budesonide)
  - **Nebulized racemic adrenaline:** VC, ↓↓ Edema (0.5 ml in 3 ml saline every 20 min.)  
[NB: Racemic epinephrine is not available in Egypt, l-epinephrine is also effective]
  - **Avoid:** Sedatives (↓↓ Conscious level) & bronchodilators (↑↑ O<sub>2</sub> requirement)

## Epiglottitis

- ☒ **Etiology:** Hemophilus influenza type b (Now rare, why?), Streptococci
- ☒ **Age:** 3-6 years
- ☒ **C/P:** Fever, toxicity, stridor, drooling, dysphagia, dysphonia, dyspnea, No barking cough
- ☒ **Lateral neck X-rays:** Thumb sign (Swollen epiglottis)
- ☒ **Medical emergency, why?**
- ☒ **Treatment:** ETT is indicated regardless the degree of apparent RD (Usually for 2-3 days)  
Antibiotics: Ceftriaxone or (Ampicillin-sulbactam)
- ☒ **Prognosis:** 6% (Without artificial airway) & 1% (With artificial airway)

## Chocking (FB Airway obstruction)

### Definition

Partial or complete obstruction of the airways (By foods or small objects)

### Incidence

Common in late infancy & early childhood, Why?

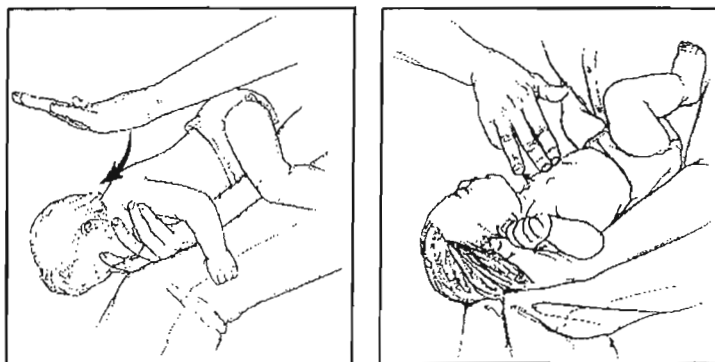
Common in unconscious patients

### When to suspect

Sudden onset of cough, chocking & cyanosis

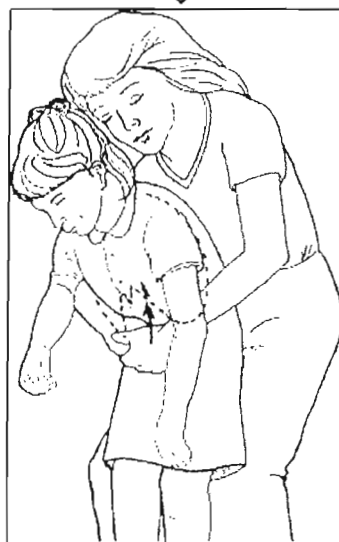
### Management

Infants



**5 Back blows AND 5 Chest thrusts**

Children



**Abdominal thrust**

# Respiratory Failure

## Definition

- Failure of the respiratory system to maintain adequate levels of O<sub>2</sub> & CO<sub>2</sub>
- Most pediatric cardiac arrest begins as respiratory failure

## Incidence

- Commoner in infants & young children, Why?
  - **Airways:** Narrower & less supported
  - **Respiratory center:** Immature

## Classification (= Types)

	<b>Lung Failure</b>	<b>Pump Failure</b>
<b>Synonyms</b>	<ul style="list-style-type: none"> <li>▪ Type I respiratory failure</li> <li>▪ Peripheral respiratory failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Type II respiratory failure</li> <li>▪ Central respiratory failure</li> </ul>
<b>Basic Defect</b>	<b>Oxygenation defect</b>	<b>Ventilation defect</b>
<b>ABG</b>	Hypoxemia (< 50 mmHg) ± Hypercapnia ± Metabolic acidosis	Hypercapnia (> 60 mmHg) ± Hypoxemia ± Respiratory acidosis
<b>C/P</b>	Respiratory distress (4 grades) 1. <b>Tachypnea</b> & working ala nasi 2. <b>Retraction</b> (Intercostal & subcostal) 3. <b>Grunting</b> (forced expiration against closed glottis) 4. <b>Cyanosis</b>	<u>Shallow, irregular, gasping</u> breathing with periods of <u>apnea</u> ± Cyanosis
<b>Therapy</b>	O <sub>2</sub> therapy ± Ventilation	Ventilation ± O <sub>2</sub> therapy
<b>Causes</b>	<b>A. Airway disease</b> <ul style="list-style-type: none"> <li>▪ Choanal atresia</li> <li>▪ Laryngomalacia</li> <li>▪ Epiglottitis</li> <li>▪ FB inhalation</li> <li>▪ Vocal cord paralysis</li> </ul> <b>B. Lung pathology</b> <ul style="list-style-type: none"> <li>▪ Bronchiolitis</li> <li>▪ Bronchiolitis obliterans</li> <li>▪ Bronchial asthma</li> <li>▪ Pneumonia</li> <li>▪ Pneumothorax</li> <li>▪ Pleural effusion</li> <li>▪ Pulmonary edema</li> <li>▪ Massive lung collapse</li> <li>▪ Cystic fibrosis</li> <li>▪ RDS, BPD</li> <li>▪ Meconium aspiration</li> <li>▪ ARDS</li> </ul>	<b>A. Severe brain pathology</b> <ul style="list-style-type: none"> <li>▪ CNS infection</li> <li>▪ ICH</li> <li>▪ CNS infarction</li> <li>▪ Trauma &amp; Tumors</li> <li>▪ CNS depressants</li> <li>▪ Central hypoventilation syndrome</li> </ul> <b>B. Neuro-muscular apparatus</b> <ul style="list-style-type: none"> <li>▪ <b>AHC:</b> Werdnig-Hoffmann disease Poliomyelitis</li> <li>▪ <b>Nerve:</b> Guillain-Barré syndrome</li> <li>▪ <b>N/M:</b> Myasthenia gravis</li> <li>▪ <b>Muscle:</b> Myopathy</li> </ul> <b>C. Thoracic cage</b> <ul style="list-style-type: none"> <li>▪ Kyphoscoliosis</li> <li>▪ Asphyxiating thoracic dystrophy</li> <li>▪ Diaphragmatic hernia</li> <li>▪ Diaphragmatic eventration</li> </ul> <b>D. Respiratory muscle fatigue (Type I)</b>

## Pathophysiology of RF

- Inspired gas composition
- Alveolar gas composition
- Alveolar ventilation & dead space ventilation
- Diffusion

# Respiratory Distress

## Definition of RD

- Abnormal respiratory pattern (dyspnea, tachypnea, nasal flaring, retractions, grunting...)
- Respiratory failure can be present without RD (abnormalities of CNS or N/M disease)
- RD can occur without respiratory disease

## Causes of RD

A) **Pulmonary causes:** "Causes of type I respiratory failure"

B) **Extrapulmonary causes**

- ☒ Acute congestive HF: Tachycardia + Tachypnea + Tender hepatomegaly
- ☒ Acute metabolic acidosis: Acidotic breathing (Rapid & deep) e.g., DKA, RTA.
- ☒ Acute severe anemia: Acute hemolytic crisis e.g., G-6-PD deficiency...
- ☒ Sepsis: Due to acidosis & ↑↑ RC

## Grades of RD

1. Tachypnea & working ala nasi
2. Retraction
3. Grunting (Forced expiration against closed glottis)
4. Cyanosis:
  - Occurs after failure of all previous compensatory mechanisms
  - Indicates  $\text{PaO}_2 < 35 \text{ mmHg}$

# Oxygen Therapy

## Indications & Dosage of Oxygen

1. Respiratory failure (40-100 %)
2. Cardiovascular failure (40 %)
3. Neurological failure (40 %)

### **Remember**

Normal  $\text{O}_2$  concentration  
in atmosphere = 21 %

## Methods of administration

Method	Age group	Comments
Incubator	Neonates	$\text{FiO}_2$ can be determined by $\text{O}_2$ analyzer
Head box	Neonates & Infants	
Simple oxygen mask	All ages	$\text{FiO}_2$ can not be determined
Venturi oxygen mask	All ages	Precise $\text{FiO}_2$ can be delivered
Nasal prongs (cannula)	All ages	$\text{FiO}_2$ can not be determined [ $\text{FiO}_2 = 21 + \text{Flow} \times 3$ ]
Ambu bag with (Mask or ETT)	All ages	Delivers 40 % $\text{O}_2$ (If no reservoir) Can deliver 100 % $\text{O}_2$ (If connected to reservoir)
Flow inflating bag (= Anesthesia bag)	All ages	Delivers 100 % $\text{O}_2$ (at all times)
ETT	All ages	Can deliver 100 % $\text{O}_2$

## Monitoring of oxygen therapy

$O_2$  Sat of  $< 85\%$  = ?? hypoxemia

### A) Clinical

- ☒ **Color:** Pink
- ☒ **Work of breathing:** Severity of respiratory distress (Grades)

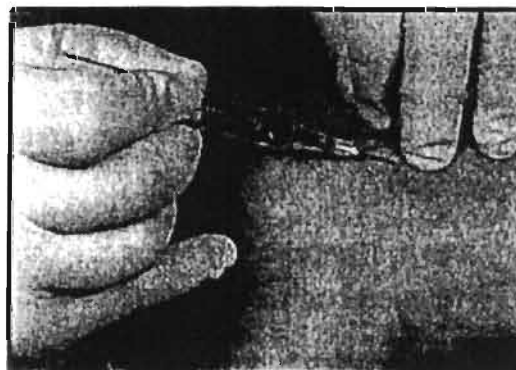
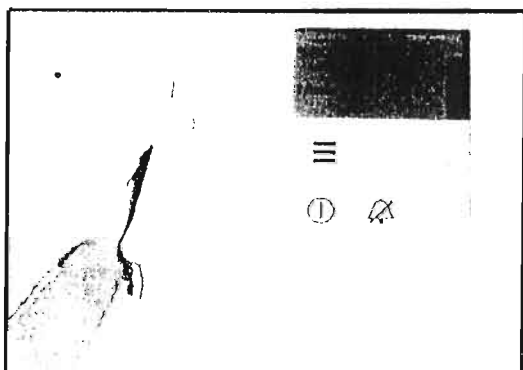
B) **Pulse Oximeter:** Good response if  $O_2$  Saturation  $> 90\%$

C) **Arterial blood gases:** Good response if  $O_2$  pressure  $> 80$  mmHg

## Pulse oximeter Vs ABG

Capnography (= End-tidal  $CO_2$  measurement)

	<b>Pulse Oximeter</b>	<b>ABG</b>
<b>Value</b>	Bed-side (Continuous)	Gold standard for assessment
<b>Parameter</b>	$O_2$ Saturation	$O_2$ Tension (& Saturation)
<b>Technique</b>	Rapid non-invasive	Arterial puncture
<b>Unit</b>	Percent	mmHg
<b>Good response</b>	$O_2$ Saturation $> 90\%$	$O_2$ Tension $> 80$ mmHg
<b>Hypoxemia</b>	Mild (90-95 %), Moderate (85-90 %)	$< 70$ mmHg
<b>Severe hypoxemia</b>	$< 85\%$	$< 50$ mmHg
<b>Errors</b> (= False results)	<ul style="list-style-type: none"> <li>▪ Peripheral coldness</li> <li>▪ Poor peripheral perfusion</li> <li>▪ Methemoglobinemia</li> <li>▪ Optical interference</li> </ul>	<ul style="list-style-type: none"> <li>▪ Venous samples</li> <li>▪ Clots or air in the sample</li> </ul>



## Complications of oxygen

- A) **Eye:** Retinopathy of prematurity
- B) **Lungs:** Bronchopulmonary dysplasia
- C) **Oxygen dependence:** Difficult weaning

- 100%  $O_2$  is toxic to the lungs in 4 hrs
- 70%  $O_2$  is toxic to the lungs in 4 days
- 40%  $O_2$  is safe for 4 weeks

## Indications of Mechanical Ventilation

1. Apnea
2. Hypoxemia:  $PaO_2 < 50$  mmHg (in spite of  $FiO_2 = 70\%$   $O_2$ )
3. Hypoxemia:  $O_2$  Saturation  $< 85-90\%$  (in spite of  $FiO_2 = 70\%$   $O_2$ )
4. Hypercarbia:  $PaCO_2 > 60$  mmHg (Hypoventilation)
5. Work of breathing (Respiratory muscle fatigue)
6. Therapeutic hyperventilation ( $\uparrow\uparrow$  ICT)
7. Supportive:
  - Shock
  - After major surgery
  - Status epilepticus
  - After cardiopulmonary resuscitation (CPR)

**Assessment of severity of lung pathology (=O<sub>2</sub> derived pulmonary indices)****1. PaO<sub>2</sub>/FiO<sub>2</sub>:** Normally it is 400-450

- Values < 300: consistent with acute lung injury
- Values < 200: consistent with ARDS

**2. Oxygenation index (OI)**

- Values between 1-5: Mild lung pathology
- Values between 6-10: Moderate lung pathology
- Values > 20: Severe lung pathology (High mortality)

$$OI = \frac{MAP \times FiO_2 \times 100}{PaO_2}$$

**3. Ventilation index (VI)**

$$VI = \frac{PIP \times Rate \times PaCO_2}{1000}$$

**Approach to a child with RF****Rules**

- Initiate investigations in order of priority
- Simultaneous intervention & investigation

**Components****A) Assessment**

- ☒ History
- ☒ Examination
- ☒ Investigations

**B) Respiratory Monitoring****C) Respiratory support**

- ☒ Airway patency: Oropharyngeal or nasopharyngeal
- ☒ Oxygen therapy: *See before*
- ☒ Inhaled gases:
  - Helium-oxygen "Heliox" (Helium is less dense than N<sub>2</sub>)
  - Nitric oxide: Inhaled pulmonary vasodilator
- ☒ Chest Physiotherapy & Suction
- ☒ PPV
  - CPAP: High-flow nasal cannula (Flow = 4-16 L/min)
  - CPAP: tight-fitting face mask
- ☒ ETT & mechanical ventilation
- ☒ ECMO

**D) Specific Therapy**

Pneumonia		Anemia	
Asthma		Acidosis	
Pneumothorax		Stridor	
Pleural effusion		RDS	
Pulmonary edema		GBS	

# Endotracheal Intubation

## Indications of ETT

1. Persistent hypoxemia or hypercarbia (*despite the above mentioned interventions*)
2. Airway patency (Goiter, micrognathia)
3. Tracheal suction (Meconium aspiration syndrome)
4. Ineffective bag & mask ventilation
5. Drugs e.g., adrenaline...
6. Surfactant therapy (in respiratory distress syndrome)
7. Prolonged ventilation is needed (as in diaphragmatic hernia)

## Internal diameter of ETT

$$ID = (Age \text{ (yr)}/4) + 4$$

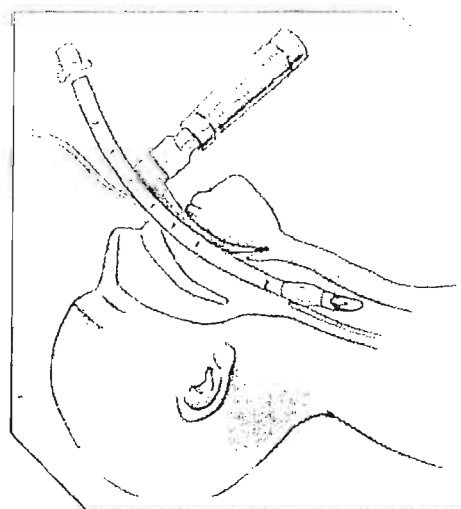
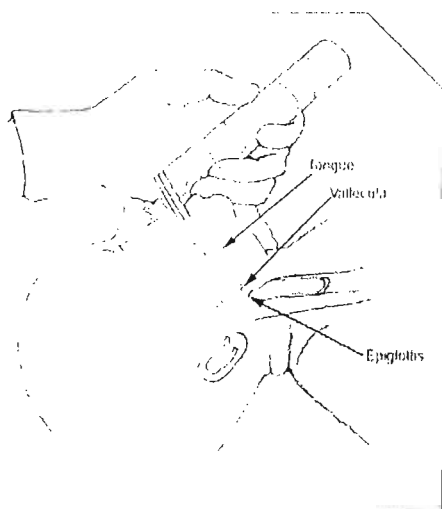
## Sedation

- Sedation & paralysis should be considered standard (unless contraindicated)

Category	Drug	Dose	Duration	Comment
Sedatives	Midazolam	0.1 mg/Kg IV	60 min	Amnesia, ↓↓ RC
	Ketamine	1-2 mg/Kg IV	10-15 min	↑↑ HR, ↑↑ BP
Analgesics	Fentanyl	2-5 µg/Kg IV	60 min	↓↓ RC
	Morphine	0.1 mg/Kg IV	120 min	↓↓ RC
N/M blocking agents	Pancuronium	0.1 mg/Kg IV	30 min	↑↑ HR

## Check position of ETT

- Seeing the ETT through the vocal cords
- Chest expansion
- Misting of ETT
- No sounds over the epigastrium
- Equal breath sounds
- CO<sub>2</sub> detector or capnography



# **Sudden Death**

## **(In Infants, Children & Adolescents)**

### **Incidence**

- 1-6 per 100.000 per year in children
- It may be traumatic\* (Occupational, vehicle or violent deaths) or nontraumatic (Cardiac\*)
- 65% of sudden deaths are due to cardiac causes

### **Causes**

#### **1. Sudden infant death syndrome**

#### **2. Myocardial disease**

- Cardiomyopathy
  - Hypertrophic, Dilated & Restrictive cardiomyopathy
  - Arrhythmogenic right ventricular dysplasia
- Myocarditis

#### **3. Coronary arterial disease**

- Anomalous origin
- Anomalous course
- Myocardial infarction
- Kawasaki disease

#### **4. Congenital heart diseases**

- Aortic stenosis
- Tetralogy of Fallot
- Transposition of great vessels
- Hypoplastic left heart syndrome
- Duct-dependent CHD
- Mitral valve prolapse
- Eisenmenger syndrome

#### **5. Conduction system (Arrhythmias)**

- Long Q-T syndrome
- Pre-excitation syndromes (e.g., WPW syndrome...)
- Heart block
- Commotio cordis ➡

#### **6. Other causes**

- Pulmonary embolism
- Pulmonary hypertension
- Child abuse
- Electrolyte disturbances
- Anorexia nervosa
- Cocaine & other stimulants
- Inborn errors of metabolism
- Heat stroke

#### **Commotio cordis**

**Etiology:** Blunt chest trauma

**Mechanism:** Ventricular fibrillation

**Pathology:** No cardiac trauma

**Prognosis:** 90% mortality

#### **Apparent Life threatening events (ALTE)**

- **CNS:** AV malformation, seizures, chiari crisis
- **Cardiac:** *as before*
- **Pulmonary:** Aspiration, pulmonary hypertension, pulmonary embolism
- **GIT:** GE, dehydration, GERD, pancreatitis
- **Endocrine/Metabolic:** CAH, hyperammonemia, GSD type 1, malignant hyperpyrexia
- **Infection:** Meningitis, encephalitis, hepatitis, pyelonephritis, botulism, pertussis, sepsis
- **Trauma:** Child abuse, Munchausen syndrome by proxy
- **Poisoning:** Salicylates, insulin, cocaine, carbon monoxide



# Sudden Infant Death Syndrome

## Definition

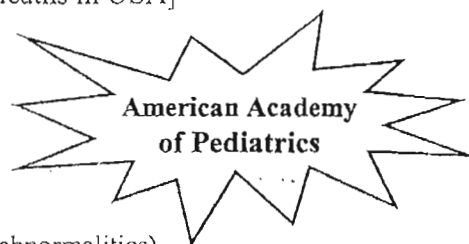
Sudden death of an infant under 1 year of age which remains unexplained after a complete post-mortem examination (DD: congenital anomalies, infection & child abuse)

## Incidence

- 0.5 per 1.000 per year (The rate declined **after 1992**, the year in which AAP recommended **Back to Sleep**)
- The 3<sup>rd</sup> leading cause of infant mortality [8% of all infant deaths in USA]

## Pathology

- Petechial hemorrhages
- Pulmonary edema
- Markers of low grade asphyxia
- Higher expression of VEGF in the CSF
- Ventral medulla: Arcuate nucleus hypoplasia (& receptor abnormalities)
- Neuronal & receptor abnormalities



## Risk Factors

### 1. Genetic factors

- Cardiac channelopathies:
  - Sodium cardiac ion channel genes
  - Potassium cardiac ion channel genes
- Serotonin transporter protein
- Genes related to autonomic nervous system development
  - MAO, Tyrosine hydroxylase
  - PHOX2A, PHOX2B
- Genes related to infection & inflammation
  - Complement C4A, Complement C4B, IL-10, IL-6, TNF- $\alpha$ , VEGF
- Genes related to energy production
  - Mitochondrial DNA polymorphisms

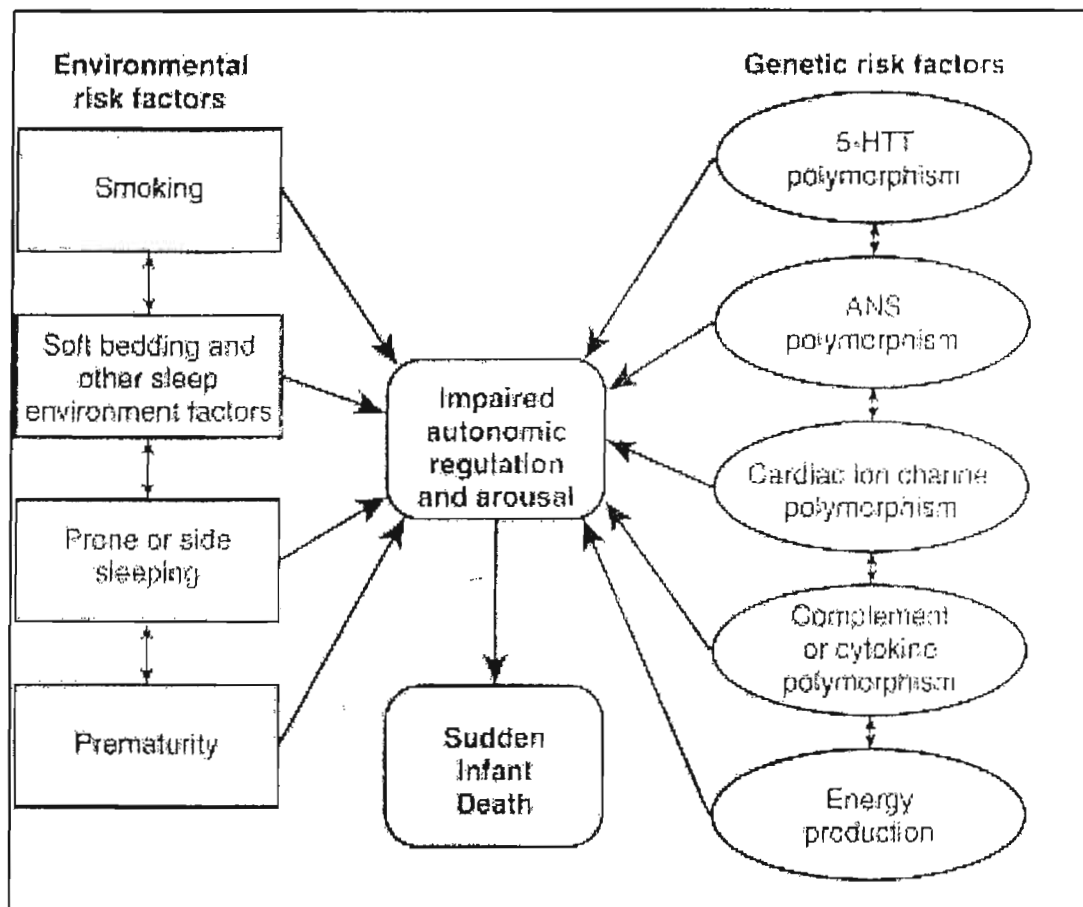
### 2. Environmental factors

Maternal & Antenatal	Infant
<ul style="list-style-type: none"> <li>▪ <math>\downarrow\downarrow</math> Age, <math>\downarrow\downarrow</math> Education, <math>\downarrow\downarrow</math> SE level</li> <li>▪ <math>\downarrow\downarrow</math> Nutrition</li> <li>▪ Smoking</li> <li>▪ Alcohol</li> <li>▪ Drugs (cocaine, heroin)</li> <li>▪ IU hypoxia</li> <li>▪ IUGR</li> </ul>	<ul style="list-style-type: none"> <li>▪ Age: Peak 2-4 months, Male sex</li> <li>▪ Growth failure</li> <li>▪ Prematurity</li> <li>▪ Prone &amp; side sleep position</li> <li>▪ Bed sharing, soft sleeping surfaces</li> <li>▪ No breastfeeding, No pacifiers</li> <li>▪ Cold seasons (No central heating)</li> </ul>

- Breastfeeding & pacifiers  $\downarrow\downarrow$  risk of SIDS
- Supine except in specific situations

## Infants at increased risk of SIDS

- Infants with ALTE
- Siblings of a SIDS victim
- Prematurity
- Genetic & environmental risk factors



### Reducing the Risk of SIDS [As recommended by the AAP]

1. **Supine position** (Prone & side sleeping are not recommended)
2. **Firm mattress** (Avoid soft mattresses)
3. **Sleeping in the parent room** (But in their own crib)
4. **Use blankets with holes**
5. **Avoid soft materials** in the infant's sleep environment (e.g., pillows...)
6. **Avoid bed sharing** (specially if the parents are tired or taking drugs)
7. **Avoid overheating**
8. **Avoid smoking**
9. **No need to use** devices to maintain sleep position
10. **No need to use** respiratory, cardiac or O<sub>2</sub> saturation home monitors
11. Consider offering a **pacifier** at bedtime. The pacifier should be used when placing the infant down for sleep and not be reinserted once it falls out. For breast-fed infants, delay introduction of the pacifier until breast-feeding is well established

# Obstructive Sleep Apnea

## Definition

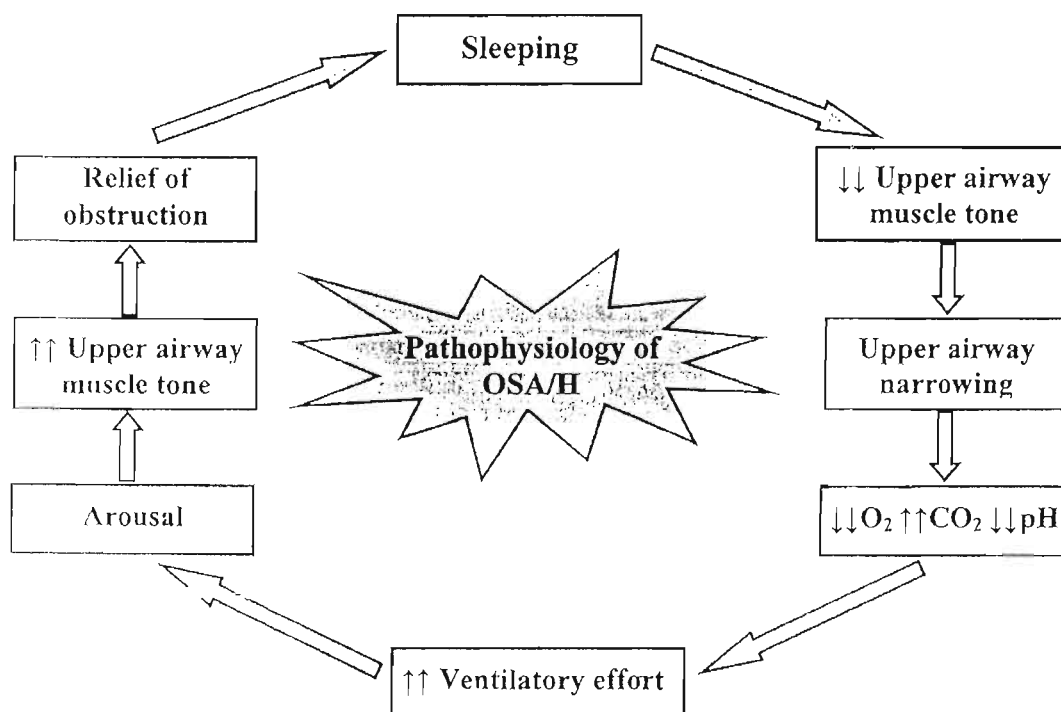
- Repeated episodes of airflow obstruction at the upper airway (Nose & mouth) during sleep
- It is usually due to adenotonsillar hypertrophy
- OSA is part of the spectrum of sleep-disordered breathing (SDB) that also includes:
  - Primary snoring: No ventilatory abnormalities (hypoxia & hypercapnia)
  - Upper airway resistance syndrome: Partial obstruction, snoring & frequent arousal
  - Obstructive hypoventilation (Hypopnea): 50% reduction of airflow
  - Sleep apnea: Complete cessation of airflow; which may be:
    - o **Central:** No chest wall movement + No airflow
    - o **Obstructive:** Chest wall movement + No airflow
    - o **Mixed**

## Incidence

- Occasional snoring: 20 %
- Every night snoring: 10 %
- OSA: 1-3 % of pre-school children

## Pathophysiology

- Airway obstruction  $\Rightarrow$  Hypoxia & hypercapnia  $\Rightarrow$  Arousal



## Other Effects (= Complications)

- Chronic hypoxia: Polycythemia, growth failure
- Increased pulmonary artery pressure, RV hypertrophy & Cor-pulmonale
- Arrhythmias

## Predisposing Factors

Anatomic	Functional
<p><b>A) Nose</b></p> <ul style="list-style-type: none"> <li>Anterior nasal stenosis</li> <li>Choanal atresia</li> <li>Deviated nasal septum</li> <li>Nasal polyps</li> <li>Rhinitis</li> </ul> <p><b>B) Mouth, Nasopharynx &amp; Oropharynx</b></p> <ul style="list-style-type: none"> <li>Macroglossia</li> <li>Cleft palate repair</li> <li>Adenotonsillar hypertrophy****</li> </ul> <p><b>C) Craniofacial</b></p> <ul style="list-style-type: none"> <li>Achondroplasia</li> <li>MPS</li> <li>Micrognathia</li> <li>Pierre Robin syndrome</li> </ul>	<p><b>A) REM sleep-related pharyngeal hypotonia</b></p> <p><b>B) Neurological causes</b></p> <ul style="list-style-type: none"> <li>Generalized hypotonia (Down...)</li> <li>Cerebral palsy</li> <li>Chiari malformation</li> <li>CNS injury: Hypoxia, trauma, tumors</li> <li>Autonomic dysfunction</li> </ul> <p><b>C) Drugs</b></p> <ul style="list-style-type: none"> <li>Sedatives: Chloral hydrate...</li> <li>Narcotics</li> <li>Anesthetics</li> </ul> <p><b>D) Other causes</b></p> <ul style="list-style-type: none"> <li>Obesity</li> <li>Dysphagia</li> <li>Excessive oral secretions</li> </ul>

## Clinical Picture

### **A) During Sleep**

- Snorting
- Mouth breathing
- Apneic attacks
- Frequent arousals
- Unusual sleeping positions

### **B) Daytime**

- Sleepiness
- Morning headaches
- Learning problems
- Behavioral changes

### **C) Physical Examination**

- Adenoid facies ➡
- Other predisposing factors (*Mention*)

#### **Adenoid Facies**

- Elongated face
- Narrow pinched nostrils
- Mouth breathing
- Short upper lip
- Infraorbital darkening

**The gold standard for  
is Polysomnogram**

## Diagnosis

### **☒ Overnight Polysomnogram**

- **Gold standard** for diagnosis [In practice, Not all children require sleep studies]
- Study of sleep physiologic variables
- Sleep stages, eye movements, muscle tone, airflow, heart rate, O<sub>2</sub> saturation

### **☒ Other investigations**

- Lateral neck X-rays
- CBC
- CXR, ECG & Echocardiography
- ABG, defect?

## Treatment

### 1. Adenotonsillectomy

- It is the **First line of treatment**
- Adenoid may **grow back**, How?
- **↑↑ Risk of postoperative complications with:** Obesity, age (< 2 yrs), hypotonia

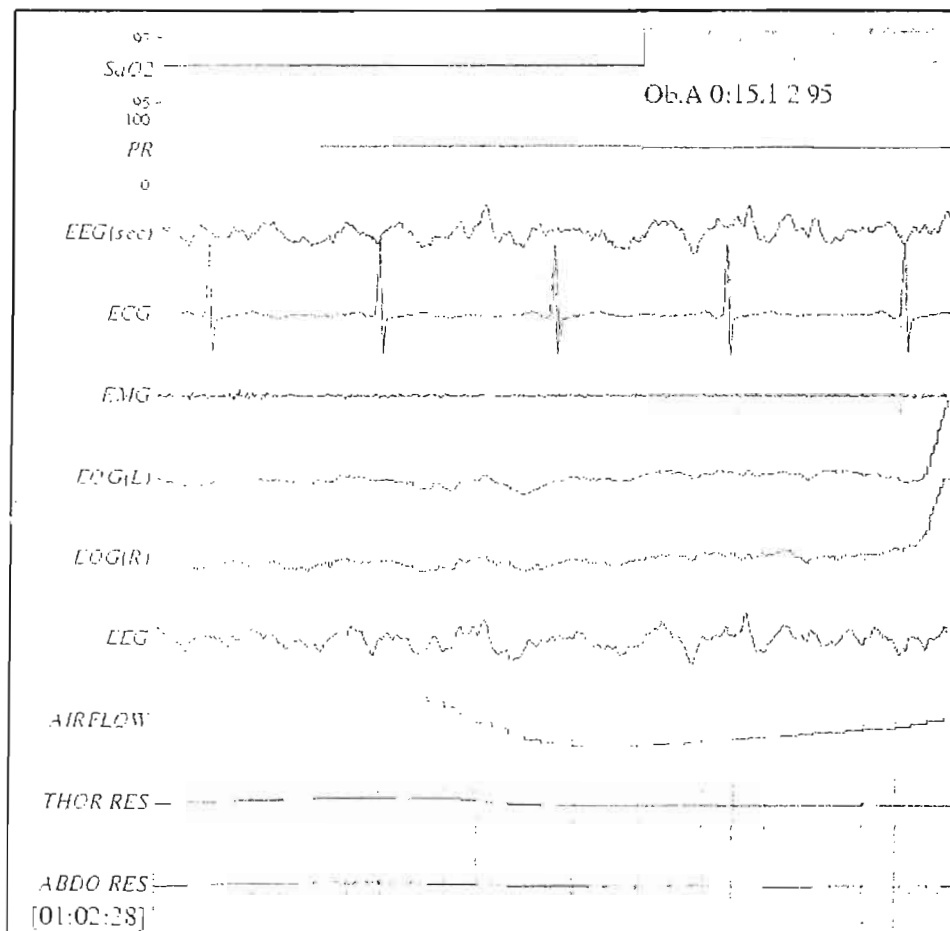
### 2. Weight reduction

### 3. Medical therapies

- Nasopharyngeal airway
- Nasal mask CPAP
- Supplemental O<sub>2</sub>
- Drugs
  - Topical nasal steroids
  - Antibiotics
  - Nasal decongestants (*Short-term* effect)

### 4. Surgical therapies

- Craniofacial surgical procedures
  - Mandibular plastic surgery
  - Choanal atresia
  - Cleft palate revision procedures
- Uveolopalatopharyngoplasty
- Correction of deviated nasal septum
- Nasal polypectomy
- Traheostomy



# **Disorders of the Nose**

## **Introduction**

- Most neonates are obligatory nose breathers (Variable)
- Nasal congestion is common in the 1<sup>st</sup> yr of life
- The internal nasal airway doubles in size in the 1<sup>st</sup> 6 months of life
- Nose is important in warming & humidification of inspired air
- Nasal mucosa is ciliated
- Nasal secretions contain lysozyme, IgA, lactoferrin, histamine & glycoproteins (Viscid)

## **Choanal Atresia**

### **Definition & Types**

- Septum between the nose & pharynx
- Unilateral or bilateral, bony (90%), membranous (10%) or combined
- CHARGE syndrome: Coloboma, Heart, choanal Atresia, Retardation, Genital, Ear anomalies

### **Incidence**

- 1: 7.000 live births

### **Clinical Picture**

- Unilateral cases may be asymptomatic for long duration (nasal discharge or obstruction)
- Bilateral cases: RD & cyanosis (Improves with crying)

### **Investigation**

- Firm catheter
- Fiberoptic rhinoscopy
- CT

### **Treatment**

- Stabilization: Oral airway & feeding
- Surgical repair: Transnasal (Restenosis is common; Mitomycin C)

**Perforation of the Septum:** Usually acquired; Syphilis, TB, CPAP

**Congenital midline nasal masses:** Dermoid, glioma, encephalocele, hemangioma

## **Nasal Foreign Body**

### **Complications**

- Infection
- Local tissue damage (batteries), perforation of the septum
- Nasal obstruction

### **Clinical Picture**

- Beads, batteries, buttons, toys, erasers
- History of FB insertion, nasal discharge, foul nasal odor, epistaxis, obstruction

### **Treatment**

- FB removal: Topical anesthesia, forceps or nasal suction

# Epistaxis

## Definition

- Bleeding from the nose
- BV of the nose anastomose on anterior part of the septum; Little's area (Kiesselbach's area)

## Etiology

### A. Local

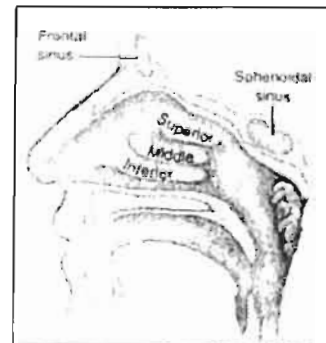
- Idiopathic (Spontaneous)
- Epistaxis digitorum
- FB
- Trauma
- Tumors (juvenile nasal angiofibroma)
- Rhinitis, sinusitis, irritants (GERD, smoking)
- Nasal polyps
- Septal deviation & perforation
- Vascular malformation
- Cocaine, topical steroids

### B. General

- Bleeding tendency: platelet, coagulopathy, liver disease,
- Hypertension
- Fever
- Drugs: NSAIDs, aspirin

## Treatment

- Compression of the nares with the child in the upright position & the head tilted forward
- Cold compresses
- Local VC (Oxymetazoline; *Afrin*)
- Nasal packing (Anterior or posterior)
- Cautery: Chemical (silver nitrate) or electrical
- Surgical



# Nasal Polyps

## Definition

- Benign pedunculated edematous nasal mucosa (affecting 0.2-1% of the population)
- They commonly arise from the ethmoidal sinus and occur in the middle meatus
- Antrochoanal polyp: arises from the maxillary antrum and can extend to the nasopharynx
- Samter's triad: Nasal polyps, aspirin sensitivity & asthma

## Etiology

- Cystic fibrosis: Commonest cause in children
- Allergic rhinitis
- Sinusitis

## Investigation

- Fiberoptic rhinoscopy, CT

## Treatment

- Local or systemic decongestants: Symptomatic
- Steroid spray. Shrinkage of the polyps
- Surgical removal

# **Common Cold**

## **(Rhinosinusitis- Nasopharyngitis)**

### **Epidemiology**

- It is the commonest infection in children (Peak: Fall & Spring)
- Young children have 6-8 colds/year (The incidence ↓↓ with age)
- Cause of recurrence: Many serotypes, superficial infection, antigenic shift & drift
- More in day-care centers

### **Etiology**

- **Viral:** Rhinoviruses, Coronaviruses, RSV, adenovirus, influenza, parainfluenza...
- **Mode of transmission:** Droplet infection & direct contact

### **Clinical Picture**

- **Fever:** Low-grade (may be absent)
- **Sore throat**
- **Nasal symptoms:**
  - Nasal discharge: Initially watery (1<sup>st</sup> few days), then mucoid
  - Nasal obstruction (Irritability & feeding difficulties)
- **DD:** Allergic rhinitis (Nasal discharge, sneezing, itching, nasal eosinophils)

### **Complications**

1. **Spread of infection**
  - Upper respiratory tract: Otitis media & sinusitis
  - Lower respiratory tract: Acute bronchitis, bronchiolitis, pneumonia
2. Precipitation of asthmatic attack in predisposed children
3. Inappropriate use of antibiotics

### **Prognosis**

- ☑ **Majority:** Benign, self-limited (1 week)
- ☑ **Complications:** Should be considered if



#### **Complications should be suspected if:**

- High / persistent fever
- Significant cough
- Persistent nasal discharge > 10 days

### **Treatment**

- Antipyretics
- Oral fluids
- Saline nasal drops ± gentle suction of the nose with a soft bulb "Before feeds"
- Nasal decongestants: Topical (oxymetazoline) or oral (adrenergic agents)
- Antihistamines: ↓↓ Rhinorrhea by 30%

## **Sinusitis**

### **Etiology**

- Viral: Following common cold
- Bacterial: Secondary infection may occur (S. pneumoniae, H. influenza, M. catarrhalis, Staph.)

### **Clinical Picture**

- Nasal symptoms, fever, headache, facial pain, periorbital edema
- Tenderness over the cheek (maxillary sinuses)
- Frontal sinusitis is uncommon, why?

### **Treatment**

- Antibiotics: Amoxicillin or amoxicillin-clavulanate (for 7 days after resolution of symptoms)
- Analgesics



# Otitis Media

## Incidence

- Acute inflammation of the middle ear
- It is the 2<sup>nd</sup> most common infection in children with peak incidence 6 months-6 yrs

## Etiology (Bacterial)

- A) **Common:** Streptococcus pneumoniae, Hemophilus influenza, Moraxella catarrhalis
- B) **Others:** Staphylococci, Streptococci, Pseudomonas

## Clinical Picture

**Ear examination is essential in every febrile child**

### A) Symptoms

- History of previous **common cold** is common
- **Fever**
- **Earache:** Unexplained irritability, crying, pulling on ears
- **Ear discharge:** With drum perforation

### B) Signs (Otoscope examination)

- Congested bulging eardrum with loss of normal light reflex
- Discharge (Perforation)

## Complications

### A) Ear complications

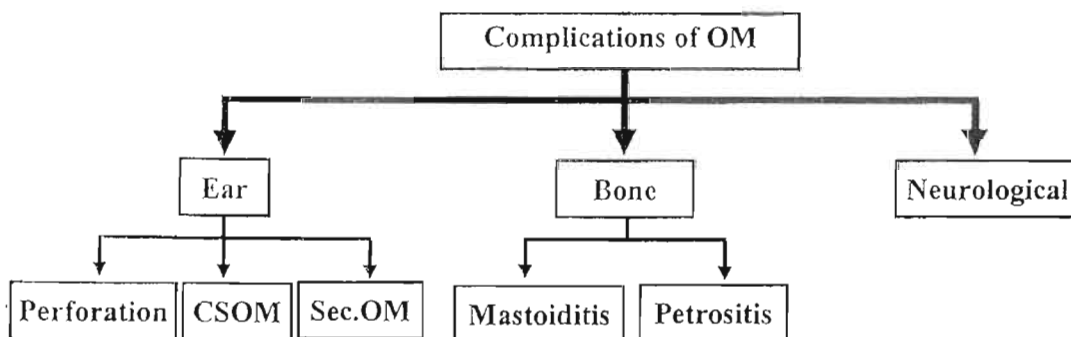
- **Drum perforation**
- **Chronic suppurative OM:** Hearing loss
- **Chronic secretory OM (OM with effusion):**
  - The commonest cause of conductive hearing loss
  - Retracted drum with lost light reflex
  - Rx options: Grommets tubes, adenoidectomy

### B) Bone complications

- **Mastoiditis:** Painful swelling behind the ear
- **Petrositis:** Inflammation of the air cells (in the petrous part of the temporal bone)

### C) Neurological complications

- **Meningitis, Encephalitis, Brain abscess**
- **Labyrinthitis:** Vestibular ataxia, vertigo
- **Lateral sinus thrombophlebitis**
- **Acute facial palsy**



## Treatment

1. Antipyretics & analgesics
2. Antibiotics: Amoxicillin or amoxicillin-Clavulanate for at least 5 days

# Pharyngitis

(Tonsillitis)

## Epidemiology

- It is a common infection in children > 2 yrs of age (Peak: Fall & Spring)
- Streptococcal pharyngitis is uncommon < 2-3 yrs

## Etiology

A) **Viral\***: Adenoviruses, coronaviruses, rhinoviruses, RSV, Coxsackie, EB virus

B) **Bacterial**: Group A  $\beta$ -hemolytic streptococci\* [M protein is the major virulent factor]

## Clinical Picture

	Viral Pharyngitis	Streptococcal Pharyngitis (Tonsillitis)
Fever	Mild-moderate	High-abrupt
Sore throat	Moderate	Severe (Difficult swallowing)
Other Symptoms	Diarrhea	Headache, abdominal pain, vomiting Rash in scarlet fever
Throat Ex.	<ul style="list-style-type: none"> <li>▪ Mild erythema of tonsils &amp; pillars</li> <li>▪ Small ulcers on the soft palate or posterior pharyngeal wall may occur</li> </ul>	<ul style="list-style-type: none"> <li>▪ Diffuse redness of tonsils &amp; pillars</li> <li>▪ Follicular exudation (<b>Follicular tonsillitis</b>)</li> <li>▪ Membrane formation (<b>Membranous tonsillitis</b>)</li> </ul>
LN	-	Enlarged tender anterior cervical LN
Cough Rhinitis Conjunctivitis Hoarseness	Common	Rare
Lab	<ul style="list-style-type: none"> <li>➤ Viral culture?</li> <li>➤ PCR?</li> </ul>	<ul style="list-style-type: none"> <li>➤ Throat culture</li> <li>➤ Rapid antigen test</li> </ul>
Treatment	No specific Rx	<ul style="list-style-type: none"> <li>➤ Oral Penicillin V: for full 10 days; (Even with early improvement)</li> <li>➤ IM Benzathine penicillin: 600,000-1,200,000 IU (Sensitivity test is required)</li> <li>➤ Oral amoxicillin for 10 days</li> <li>➤ Cephalosporin (Cephalexin)</li> </ul> <p><b>For patients allergic to penicillin</b></p> <ul style="list-style-type: none"> <li>➤ Erythromycin: 40mg/Kg/d for 10 days</li> <li>➤ Azithromycin: 12mg/Kg/d for 5 days</li> <li>➤ Clarithromycin: 15mg/Kg/d for 10 days</li> <li>➤ Clindamycin: 20mg/Kg/d for 10 days</li> </ul>
Complications	OM	<ul style="list-style-type: none"> <li>➤ Retropharyngeal abscess</li> <li>➤ Peritonsillar abscess (quinsy)</li> <li>➤ Rheumatic fever</li> <li>➤ Post-Streptococcal GN</li> </ul>

### Indications of tonsillectomy: (Controversial)

1. Recurrence  $\geq$  3-5/yr
2. Peritonsillar abscess (Quinsy)
3. Obstructive sleep apnea

**NB:** Large tonsils alone is NOT an indication

**Multivalent vaccine is under development**

# Acute Bronchitis

## Incidence

It is the most common cause of acute cough in children

## Classification

A) **Nonspecific Bronchitis:** Mostly viral

B) **Specific Bronchitis:** With measles, pertussis, diphtheria, scarlet fever

## Etiology

A) **Viral\*:** Following nasopharyngitis (Rhinoviruses...)

B) **Bacterial:** Pneumococci, Staphylococci, Hemophilus influenza

## Clinical Picture

- History of previous **nasopharyngitis** is common (3-4 days before the onset)
- **Cough**, chest pain
- **Fever:** High fever suggests bacterial etiology
- **Vomiting:** Gastric irritation, why?
- **Duration:** 2 weeks

## Stages (3 stages)

	<b>Early stage</b>	<b>Productive stage</b>	<b>Convalescent stage</b>
<b>Cough</b>	Dry Severe Metallic (Brassy) Spasmodic (with tracheitis)	Productive Less severe Rattling	Less frequent Less severe May be prolonged (2 wks)
<b>Chest Ex.</b>	Normal	Expiratory rhonchi Coarse crepitations	Chest signs disappear gradually

## Treatment

### 1. Cough medicines

- Expectorants & mucolytics may be prescribed to liquefy viscid secretion
- Drinking water is the best expectorant
- Cough suppressants should be avoided

### 2. Antibiotics:

- When bacterial bronchitis is suspected
- Amoxicillin for 5 days

### **Bacterial bronchitis is suspected if:**

- High fever
- Sick look
- Prolonged cough
- Purulent sputum

## DD: Causes of cough

# Acute Bronchiolitis

## Incidence

- It is the most common cause of RD & acute wheezing in infants resulting from inflammatory obstruction of the small airways (bronchioles)
- Age: 1<sup>st</sup> 2 yrs of life (Infancy), with peak incidence at 3-6 months (Winter)

## Etiology

- A) **Viral:** Respiratory syncytial virus (> 50% of cases), parainfluenza, adenoviruses  
 B) **Others:** Mycoplasma

## Pathophysiology

- Viral infection → Inflammation of the small airways → Obstruction (Edema & mucus)
- Obstruction is more during expiration → Expiratory wheezes
- Ventilation / Perfusion mismatch

## Clinical Picture

### A) Symptoms

- History of contact with a family member with minor respiratory illness
- Development of **nasopharyngitis** (3-4 days before the onset)
- **Cough, wheezing, dyspnea, RD, irritability** following URT symptoms
- Apnea in infants < 6 month
- Risk factors for severe disease: age < 12 wks, GA < 35wks, BPD, CHD

### B) Signs

- **RD** (Grades 1-4)
- **Expiratory wheezes**

## Investigations

- **CBC:** Normal
- **CXR:** Hyperinflation
- **Nasopharyngeal wash:** for RSV antigen detection (Sensitivity = 90%)

## Prevention

- Palivizumab (IM, monthly): Monoclonal antibody to RSV [BPD & preterm infants]
- RSV IVIG

## Treatment

### A) Mild RD: Can be managed at home

1. Careful feeding (To avoid aspiration)
2. Close observation (Degree of RD)

### B) Moderate to Severe RD &/or risk factors: Should be hospitalized

1. Oxygen therapy
2. Proper hydration: IV fluid
3. Nebulized  $\beta$ -agonists: Salbutamol [Nebulized hypertonic saline may have some benefit]
4. Steroids (Controversial)
5. Antibiotics are **not** indicated except if there is...
6. Antiviral agents (as ribavirin) may be used in infants with CHD or chronic lung disease (Not indicated in otherwise healthy infants)
7. Mechanical ventilation may be needed in severe cases (1% of cases)

## Prognosis

- **Recovery:** Usually occurs in 7-10 days
- **Mortality:** < 1%

# Cystic Fibrosis

## Definition

- Inherited multisystem disorder characterized mainly by:
  - Recurrent **chest** infections  $\Rightarrow$  Chronic lung damage (Bronchiectasis)
  - **GIT** malabsorption  $\Rightarrow$  Failure to thrive

## Molecular Genetics & Epidemiology

- Autosomal recessive (CFTR gene is located on chromosome 7q)
- It is due to a defect in CFTR (CF transmembrane regulator) protein
- There are > 1500 mutations (grouped into 5 Classes of mutations)
- Loss of phenylalanine at position 508 ( $\Delta F508$ ) is the commonest ( $\approx 75\%$ )
- **Modifier** gene polymorphisms lead to variation in disease severity (TGF- $\beta$ 1 gene)
- "Mild" mutation of CFTR can cause isolated congenital bilateral absence of the vas
- Incidence: 1/ 3,500 live births
- Highest prevalence in Northern Europeans [Carrier rate = 1:25]

### CFTR Structure & Function

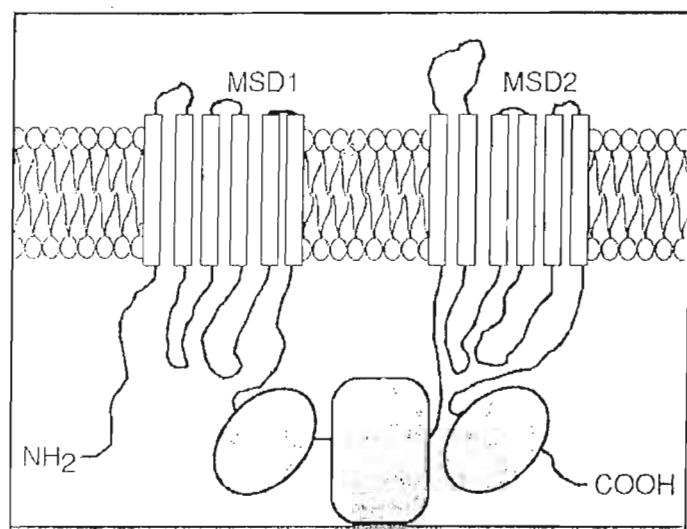
- CFTR is a glycoprotein (1480 amino acids) arranged in 5 domains
- It acts as Cl channel which is activated by phosphorylation of the R domain (cAMP-mediated)
- CFTR is located at the apical compartment of **epithelial** cells in respiratory, GIT, GU, sweat & salivary glands

### CFTR Defect:

- **Respiratory, GIT:** Defective Cl secretion &  $\uparrow\uparrow$  reabsorption of Na & water  
Viscid secretion
- **Sweat glands:** [The main function of sweat glands to absorb not to secrete Cl]  
Elevation of sweat Na & Cl (**Basis of Sweat chloride test**)
- **CFTR dysfunction:** Chloride is trapped inside the cells in the airway and outside in the skin

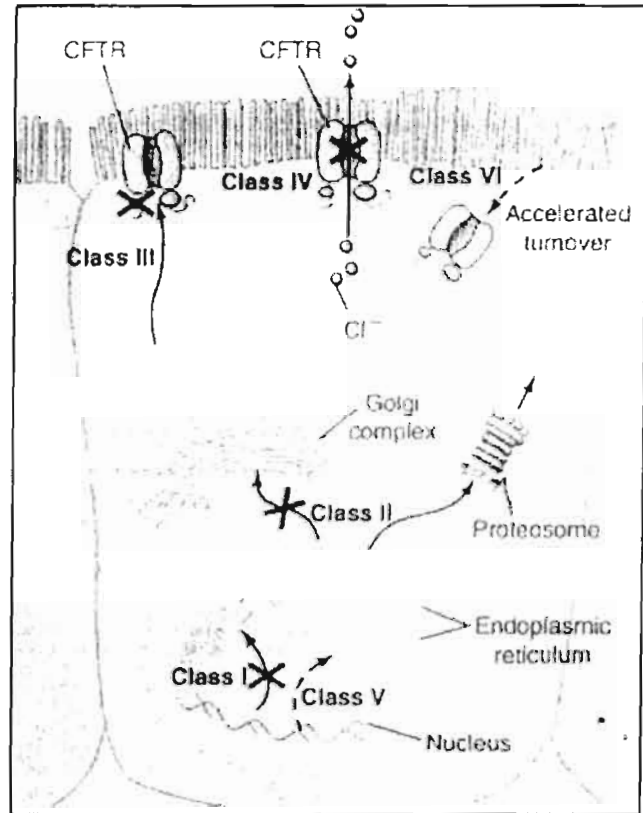
### Domains of CFTR (5):

- 2 membrane-spanning domains
- 2 nucleotide-binding domains
- 1 regulatory domain



### Categories of CFTR mutations:

- Class I: Absent protein synthesis
- Class II: Defective protein maturation
- Class III: Defective regulation
- Class IV: Defective Cl<sup>-</sup> conductance
- Class V: Defective transcription
- Class VI: Accelerated turnover



## Pathogenesis & Pathology

### ☒ Respiratory system

- Viscid secretion ( $\downarrow \downarrow$  H<sub>2</sub>O &  $\downarrow \downarrow$  HCO<sub>3</sub>), acidified surface liquid
- Difficult clearance of secretion by mucocilliary mechanisms
- Airway colonization with Staph. aureus, H. influenza, Pseudomonas, B. cepacia
- Chronic infections (nutritional deficit is a contributing factor)
- Inflammatory response (mediators) in the wall
- Airway obstruction
- Bronchitis, bronchiolitis, bronchiectasis, emphysema, pneumothorax, fibrosis
- Nose & sinuses: Epithelial hyperplasia, nasal polyps & sinusitis

### ☒ GIT

- Viscid pancreatic secretion (exocrine dysfunction) with later endocrinal dysfunction
- Pancreatic pathology: eosinophilic material & fibrosis
- Salivary gland obstruction
- GERD (Chronic cough)
- Liver dysfunction & biliary cirrhosis

### ☒ Sweat gland: Positive sweat chloride test

### ☒ Genitourinary system

- Males: Obliteration or atresia of the epididymis, vas deferens & seminal vesicles
- Females: Cervical glands are distended with mucus, endocervicitis

## Clinical Picture

### A) Respiratory Tract (*Main determinant of morbidity & mortality*)

- Cough is the most constant symptom (1<sup>st</sup> dry but then productive purulent)
- Recurrent chest infections: Staph. aureus, H. influenza, Pseudomonas, B. cepacia
- Bronchiolitis (wheezes)
- Examination: Clubbing & chest signs (shape, air entry, wheezes, crepitations)
- Complications: atelectasis, hemoptysis, pneumothorax, fibrosis, cor pulmonale
- Nasal polyps (15-20%) & chronic sinusitis

### B) Cardiovascular system

- RV hypertrophy & failure (= Cor pulmonale) is a late event

### C) Pancreas

- Exocrinal dysfunction: Maldigestion & malabsorption  $\Rightarrow$  FTT (Bulky greasy stools)
- Endocrinal dysfunction: Diabetes mellitus (2<sup>nd</sup> decade)  $\Rightarrow$  Polyuria & polydipsia
- Acute pancreatitis

### D) Intestinal Tract

- Delayed passage of meconium
- Meconium ileus in 15-20 % of neonates with CF
- Meconium peritonitis
- Meconium plug syndrome
- Distal intestinal obstruction syndrome (DIOS)
- Intussusception, fecal impaction, rectal prolapse
- Vitamin deficiency  $\Rightarrow$

**Vit A:** Keratomalacia, xerophthalmia, blindness, bitot spots, infections Thick skin  
**Vit D:** Rickets & osteoporosis  
**Vit K:** Bleeding  
**Vit E:** Hemolytic anemia, PN, myopathy

### E) Hepatobiliary

- Hepatomegaly & liver dysfunction
- Biliary cirrhosis & portal hypertension
- Biliary stones (Cholelithiasis)

### F) Sweat glands

- Hyponatremic dehydration (Salt loss)
- Hypochloremic alkalosis
- Salty taste of sweat (?kissing)

### G) Genitourinary Tract

- Male infertility is common (> 95%): Due to obstruction of the vas deferens in utero resulting in atresia or absence at birth [Azoospermia]
- Female fertility is usually maintained: Pregnancy outcome is related to general health & nutritional status of the mother

## Diagnostic Criteria of CF

### Clinical

- Typical clinical features  
OR
- Sibling with CF  
OR
- Positive neonatal screening

**PLUS**

### Laboratory

- Two positive sweat Cl test  
OR
- Two CF gene mutations  
OR
- Abnormal nasal potential difference

## Investigations

### A) Laboratory

#### 1. Sweat chloride test

- Value: Gold standard for diagnosis (**Some mutations have normal sweat chloride**)
- Technique: 100 mg sweat is needed (using pilocarpine iontophoresis)
- Results:  $Cl > 60$  (Positive), 40-60 (borderline),  $< 40$  mEq/L (normal)
- Should be repeated, why?
- False negative test: Malnutrition, dilution, certain mutation
- False positive test:
 

○ Autonomic dysfunction	○ Malnutrition	○ Hypothyroidism
○ Addison disease & CAH	○ Dehydration	○ Hypoparathyroidism (familial)
○ Anorexia nervosa	○ Nephrogenic DI	○ Eczema
○ Hypoproteinemia	○ MPS & GSD type 1	○ Ectodermal dysplasia

#### 2. Immune-reactive trypsin (IRT): $\uparrow\uparrow$ (Used $< 3$ months of age)

#### 3. Nasal potential difference: $\uparrow\uparrow$

#### 4. Neonatal screening: By IRT & limited DNA testing

#### 5. DNA testing:

- Diagnosis of CF: For the common mutations ( $\Delta F508$  & up to 30 other mutations)
  - Prenatal diagnosis
  - Carrier detection
- } mutational analysis

#### 6. CBC, ABG, electrolytes & Liver function tests

#### 7. Sputum culture (Fasting gastric aspirate, lower pharyngeal swab, bronchoscopy)

#### 8. Pulmonary function tests: Obstructive changes (Late: restrictive)

#### 9. Pancreatic function

- Diagnosis of fat malabsorption: 3-day stool collection or serum canitine
- Duodenal aspirate
- Stool elastase is  $\downarrow\downarrow$
- OGTT

### B) Imaging

#### 1. CXR, CT chest

- Hyperinflation
- Infiltrations & opacities
- Bronchial thickening
- Bronchiectasis
- Dilated pulmonary artery
- CT is sensitive to early bronchiectasis



#### 2. CT Sinuses

- Failure of frontal sinuses development
- Panopacification of sinuses

#### 3. Abdominal X-rays

- Dilated loops with air-fluid levels
- Ground-glass material in the lower abdomen
- Peritoneal or scrotal calcification



### C) Invasive

#### 1. Bronchoscopy

#### 2. GIT endoscopy



## Treatment

### A) Pulmonary therapy

#### 1. Inhalation therapy (Inhaler, spacer, nebulizer)

- Saline & hypertonic saline
- Bronchodilators
- Steroids
- Human recombinant DNase: Single daily dose (Improves pulmonary function)

#### 2. Airway clearance therapy

- Chest physiotherapy: Chest percussion & postural drainage
- Expectorants: Iodides (?efficacy)

#### 3. Antibiotics: Oral, Aerosolized or IV. Organisms??

- NB: Infection with mycoplasma & chlamydia has been documented. So, macrolides may be used empirically for flare of symptoms

	Organisms	Agents
Oral	Staph. aureus	Dicloxacillin, Cephalexin, Amoxicillin-clavulanate
	H. influenza	Amoxicillin
	Pseudomonas	Ciprofloxacin
	Burkholderia cepacia	SMZ-TMP
Aerosol		Tobramycin Gentamycin
IV	Staph. aureus	Nafcillin Vancomycin
	Pseudomonas	Tobramycin Amikacin Piperacillin Ceftazidime
	Burkholderia cepacia	Chloramphenicol

#### 4. Bronchodilators

- B-adrenergic agonists, ipratropium, cromolyn sodium

#### 5. Anti-inflammatory

- Steroids: in severe reactive airway disease & allergic bronchopulmonary aspergillosis
- NSAIDs (Ibuprofen)

#### 6. Endoscopy & lavage

#### 7. Rx of pulmonary complications

- Atelectasis
- Hemoptysis: Antibiotics, physiotherapy, vitamin K
- Pneumothorax
- Respiratory failure
- Rt sided heart failure: Diuretics
- Allergic aspergillosis: oral steroids, oral anti-fungal Rx
- Non-tuberculous mycobacterial infection

#### 8. Lung transplantation

#### 9. Nasal polyps

- Local or systemic decongestants: Symptomatic
- Steroid spray: Shrinkage of the polyps
- Surgical removal

#### 10. Rhinosinusitis: Antibiotics

**B) Nutritional therapy**

1. **Diet:** High calorie (130 Kcal/Kg/day), Low-fat diet (Elemental formula)
2. **Vitamin supplementation**
3. **Mineral supplementation:** Zinc, iron...
4. **Pancreatic enzyme replacement:** ↑↑ doses is linked to colonic stricture
5. **Recombinant GH therapy**
6. **Salt loss**
  - Sweat salt loss specially in hot weather
  - Avoid overdressing
  - Free access to salt & water

**C) GIT**

1. **Portal hypertension & liver cell failure**
2. **Meconium ileus:** Fluid intake, laxatives, gastrografin enema
3. **DIOS (Meconium equivalent)**
  - Polyethylene glycol (*Non-absorbed laxative*)
  - Large volume bowel lavage (Oral or NGT)
  - Complete obstruction: Enema
4. **Intussusception, volvulus**
5. **GERD**
6. **Pancreatitis**
7. **Diabetes mellitus**

**D) Other lines: Gene therapy****Prognosis**

- Life-limiting disease (But survival has dramatically improved)
- Males have better survival
- Activities should not be restricted, regular physical exercise should be encouraged

**Complications of Treatment**

Complication	Agent
GIT bleeding	
Hyperglycemia	
Growth retardation	
Renal dysfunction:	
Tubular	
Interstitial nephritis	
Hearing loss, vestibular dysfunction	
Peripheral neuropathy or optic atrophy	
Hypomagnesemia	
Hyperuricemia, colonic stricture	
Goiter	
Gynecomastia	
Enamel hypoplasia or staining	

# **Primary Ciliary Dyskinesia**

## **(Immotile Cilia Syndrome)**

### **Definition**

- Inherited disorder characterized by impaired ciliary function

### **Molecular Genetics & Epidemiology**

- Autosomal recessive (Rare cases are AD & XL)
- Genes involved in PCD include DNAH11 (9p) & DNAH5 (5p)
- Incidence: 1/ 20,000 live births

### **Normal Ciliary Ultrastructure and Function**

- Cilia are hair-like organelles that move fluids, mucus, and inhaled particulates
- The epithelium in the nasopharynx, middle ear, sinuses & larger airways is ciliated
- A mature ciliated epithelial cell has  $\approx 200$  uniform motile cilia
- Each cilium is a complex composed of  $\approx 250$  proteins
- Dynein (ATPase): arranged in outer & inner dynein arm
- Hydrolysis of ATP is the source of energy (ciliary movement)

### **Types of Cilia:**

- **Motile cilia:** Respiratory system
- **Primary cilia:** Immotile (Nephron, retina, bile ducts, hypothalamus)
- **Nodal cilia:** Only during embryonic development, rotational movement, body sidedness

### **Structural changes in PCD:**

- Shortening or absence of dynein arms is the most common (90%)
- Other anomalies: Microtubular transposition, ciliary agenesis, radial spoke & nexin link defects

### **Clinical Picture**

#### **A) Respiratory Tract**

- Neonatal RD
- Chronic cough
- Recurrent pneumonia
- Bronchiectasis
- Airway colonization with H. influenza, Staph. aureus, S. pneumoniae, Pseudomonas
- Ear: Chronic otitis media & hearing loss
- Rhinitis, nasal polyps & chronic sinusitis
- Examination: Clubbing & chest signs (shape, air entry, wheezes, crepitations)
- Complications: atelectasis, hemoptysis, pneumothorax, fibrosis, cor pulmonale
- The average age of diagnosis is  $> 4$  yr (*High index of suspicion is needed*)

**25% of patients with situs inversus totalis have PCD**

#### **B) Genitourinary Tract**

- Male: Immotile sperms (Typical but not always present)
- Female: Fallopian tubes

#### **C) Orientation (Laterality) defects**

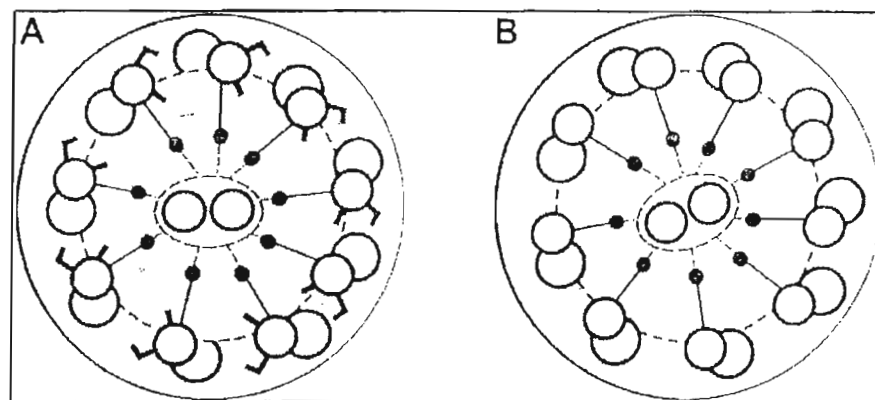
- 50% of cases have situs inversus totalis
- **Kartagener triad:** situs inversus totalis, chronic sinusitis & bronchiectasis
- **Heterotaxy** (asplenia, polysplenia, CHD)

#### **D) CNS**

- Hydrocephaly, why?
- Retinitis pigmentosa

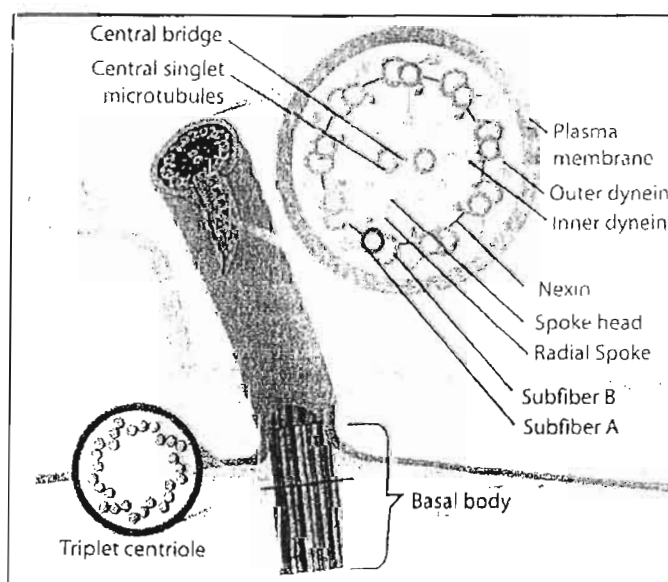
## Investigations

- CXR & CT chest
- CT Sinuses
- Electron microscopy:
  - The **gold standard** to assess ciliary ultrastructural defects
  - Nasal epithelium or bronchial brushing can provide an adequate specimen
  - Ciliary defects can be acquired, how?
  - Normal ultrastructure does not exclude PCD
- Qualitative tests to assess ciliary function: Saccharin test
- Exhaled NO concentration ( $\downarrow\downarrow$  in PCD)
- Ciliary beat frequency measurements
- High-resolution, high-speed, digital imaging of ciliary motion
- Genetic testing



## Treatment (No specific Rx)

- Airway clearance therapy
- Activities should not be restricted, regular physical exercise should be encouraged
- Bronchodilators
- Antibiotics
- Sinus & ear



## Cilopathies:

- PCD
- Bardet-Biedl syndrome
- Polycystic kidney and liver disease
- Nephronophthisis
- Joubert syndrome
- Senior-Loken syndrome
- Alstrom syndrome
- Meckel-Gruber syndrome
- Asphyxiating thoracic dystrophy
- Some forms of retinal degeneration
- Some forms of hydrocephaly

# Emphysema & Overinflation

## Definitions

- **Emphysema:** Distension of the air spaces with destruction of the alveolar walls (Irreversible)
- **Overinflation:** Distension of the air spaces  $\pm$  destruction of the alveolar walls (Reversible)
- **Compensatory overinflation:** Occurs in normal lung tissue 2ry to pneumonia, collapse...
- **SC emphysema:** Air in the SC tissue (Pneumothorax, tracheostomy, fracture orbit, asthma, trauma, toracocentesis...). Crepitus, self-limited condition, No specific Rx
- **Obstructive overinflation:** 2ry to partial obstruction (Ball-valve mechanism) by FB, thick mucus, LN, tumors, TB...

## A. Localized Obstructive Overinflation

### a. Unilateral pulmonary emphysema (Macleod syndrome):

- Postinfectious; following pneumonia or obliterative bronchiolitis (?Adenovirus)
- Pathogenesis: Arrest of alveolar growth & hypoplasia of pulmonary vessels
- Radiology: Small & hyperlucent lung with overexpansion of the contralateral lung

### b. Congenital lobar emphysema

- **Etiology:**
  - Deficient bronchial cartilage
  - Obstruction (aberrant vessel, mucosal flap)
  - Familial cases have been reported
- **Pathology:**
  - Left upper lobe is the commonest to be affected
  - Collapse of the ipsilateral normal lung & compression on the opposite lung
  - Mediastinal shift & transmediastinal herniation
- **Clinical Picture:**
  - Variable degrees of RD
- **Investigations:**
  - CXR, CT, bronchoscopy, V/Q scan
  - MRA, why?
- **Treatment:**
  - Medical Rx: Selective intubation of the unaffected lung, bronchoscopy
  - Surgical excision

## B. Generalized Obstructive Overinflation

(Diffuse involvement of the bronchioles)

- **Etiology:**
  - Asthma, cystic fibrosis, bronchiolitis
- **Pathology:**
  - interstitial emphysema, pneumomediastinum & pneumothorax
- **Investigations:**
  - CXR: Hypertranslucency of both lungs
  - Transverse ribs with wide spacing
  - Low flat diaphragm
  - ↑↑ AP diameter
  - Ribbon-shaped heart
  - Pneumatocoeles →



# **$\alpha$ 1-Antitrypsin Deficiency**

## **(& Emphysema)**

### Definition

- Inherited disorder characterized by:
  - Important cause of emphysema in adults (3<sup>rd</sup> & 4<sup>th</sup> decades)
  - Important cause of liver disease in children

### Molecular Genetics & Epidemiology

- Autosomal recessive "Codominant" (A1AT gene is located on chromosome 14q)
- Incidence: 1/ 5,000 live births (*Northern Europeans*\*)

#### **A1AT Function**

- A1AT is a protease inhibitor (Pi) synthesized in the liver (> 100 variants)
- It protects tissues from enzymes of inflammatory cells (especially neutrophil elastase)
- Cigarette smoke can lead to oxidation of methionine 358 of A1AT (essential for binding elastase)
- The normal  $\alpha$ 1-AT is PiM, mutant protein is not produced (null), or abnormal (PiZ & others)
- Serum level for Enzyme phenotypes:
  - Pi MM: 100%
  - Pi MZ: 60%
  - Pi ZZ: 15%
  - Pi nullnull: 0% (No liver disease)

#### **Effects of A1AT deficiency:**

- Break down of elastin (Elasticity of the lungs), resulting in emphysema in adults and cirrhosis in adults & children

### Clinical Picture

#### A) Respiratory Tract

- Emphysema
- Smoking greatly increases the risk of emphysema
- Chronic respiratory symptoms

**No or little detectable pulmonary disease during childhood**

#### B) Hepatic

- Neonatal cholestasis, hepatomegaly, splenomegaly

#### C) Skin: Vasculitis

### Investigations

- Enzyme level: Normal: 150-350 mg/dL
- Serum electrophoresis for enzyme phenotype
- PCR for genotype
- CXR & CT chest: Emphysema
- PFTs: usually normal in children, but it can show airflow obstruction particularly in adolescents who smoke
- Neonatal screening

### Treatment

- IV enzyme replacement from pooled human plasma (A level of 80 mg/dL is protective)
- Recombinant A1AT: under trial
- Inhalation of the plasma-derived product is under evaluation
- Lung transplantation for end-stage disease

# **Congenital Anomalies of the Lung**

## **Pulmonary agenesis & Aplasia**

### **Definition**

- Pulmonary agenesis: Complete absence of a lung (No bronchial stump or carina) [AR disease]
- Bilateral pulmonary agenesis is incompatible with life
- Pulmonary aplasia: There is bronchial stump & carina

### **Incidence**

- Pulmonary agenesis: 1:10.000 live births
- Rt lung agenesis has higher mortality than the Lt
- May be associated with other congenital anomalies (VACTERL)

### **Clinical Picture**

- Manifestations are usually related to central airway complications; compression, stenosis...
- Scoliosis & thoracic asymmetry, why?

### **Investigations**

- CXR (Mediastinal shift to the same side), CT is diagnostic

### **Treatment** Supportive

## **Pulmonary Hypoplasia**

### **Definition**

- ↓↓ Number of alveoli & airway generations

### **Etiology**

- Primary
- Secondary: Oligohydramnios (*causes*), diaphragmatic hernia, CCAM, thoracic dystrophy, pleural effusion (hydrops)

### **Clinical Picture**

- RD, PPHN

### **Treatment** Supportive: RD, PPHN

## **Lung Hernia**

### **Definition**

- Herniation of the lung beyond its normal boundaries; usually cervical
- Other sites include: Parasternal, paravertebral, intercostal

### **Etiology**

- Congenital
- Acquired: Trauma, chronic cough, weak neck muscles (Trapezius, scalene muscles)

### **Clinical Picture**

- Cervical hernia: Neck soft swelling that appear with straining
- Other sites

### **Treatment**

- Rx of the cause
- Reassurance. Surgical Rx for cosmetic reasons may be needed

## Congenital Cystic Adenomatoid Malformation

### Definition

- Hamartomatous or dysplastic lung tissue mixed with normal lung confined to one lobe
- Cysts are very common (may contain cartilage)

### Types

	Type 1	Type 2	Type 3
<b>Incidence</b>	50	40	10
<b>Histology</b>	Macrocytic	Microcystic	No cysts
<b>Prognosis</b>	Good	Bad	Poorest

### Clinical Picture

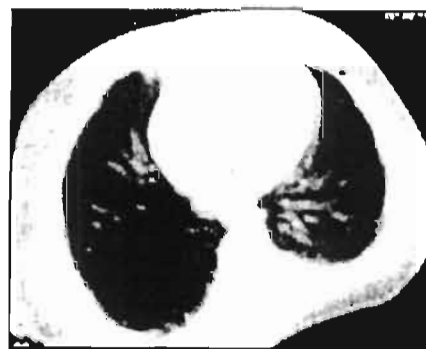
- RD, respiratory infection, pneumothorax
- Pulmonary hypoplasia may develop, why?
- May be asymptomatic for years

### Investigations

- CXR & CT (Cystic mass, DD: Diaphragmatic hernia)

### Treatment

- Antenatal Rx: Controversial
- Surgical Rx for symptomatic patients
- Surgical Rx for asymptomatic patients by 1 yr (Risk of carcinoma or sarcoma)



## Pulmonary Sequestration

### Definition

- Congenital anomaly in which part of the lung (sequestered tissue) is not connected to the normal bronchial tree & receives its arterial supply from the systemic arteries (not pulmonary)
- It may be intralobar or extralobar

### Types

	Intralobar	Extralobar
<b>Incidence</b>	75%	25%
<b>Onset</b>	Adolescence	Infancy
<b>Site</b>	Lower lobe	Left lung (90%)
<b>Visceral pleura</b>	Covered with the same pleura	Has its own pleura
<b>Sex</b>	M = F	M > F (80%)
<b>Venous drainage</b>	Pulmonary veins (LA)	IVC (RA)
<b>Infection</b>	Common	Rare
<b>Associations</b>	Rare	CCAM, CDH, pulmonary hypoplasia CHD, vertebral & colonic duplication
<b>Picture</b>	<p>IPS</p> <p>Anomalous artery</p>	<p>EPS</p> <p>Anomalous artery</p>

Investigations CXR, CT, MRA

Treatment Surgical excision



## **Bronchogenic Cysts**

### **Definition**

- Cysts due to defective growth of the embryologic lung bud
- Lined with ciliated epithelium
- Commonly on the Rt side near midline (trachea, esophagus, carina)

### **Clinical Picture**

- Compression: RD, cough, pain, dysphagia
- Infection

### **Investigations** CXR & CT

### **Treatment** Surgical excision

## **Pulmonary AV Fistula**

### **Definition**

- The usual communication is between the pulmonary artery and pulmonary vein
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia): The commonest
  - AD disease
  - Telangiectasia (Skin, GIT, nose): Epistaxis, GIT bleeding, anemia
  - AVM: Lung, liver (HF, portal HTN, encephalopathy), brain (Headache & bleeding)

### **Clinical Picture**

- Large fistulas: RD, cyanosis, clubbing, continuous murmur, polycythemia, hemoptysis
- CNS complications: Cerebral thrombosis, abscess
- Cardiomegaly and heart failure are not present, why? "*Low pressure fistula*"

### **Investigation**

- CXR & fluoroscopy
- Pulmonary angiography

### **Treatment**

- Surgical excision (lobectomy)

# Pulmonary Edema

## Definition

- Excessive accumulation of fluid in the interstitial & intra-alveolar spaces of the lungs
- Sequences: Desaturation,  $\downarrow\downarrow$  lung compliance, RD
- Traditionally classified into: Cardiogenic & non-cardiogenic

## Etiology

### A) $\uparrow\uparrow$ Pulmonary capillary pressure

- **Cardiogenic:** LV failure & mitral valve disease
- **Non-cardiogenic:** Pulmonary venoocclusive disease, mediastinal tumor

### B) $\uparrow\uparrow$ Capillary permeability (*Direct or Mediators; TNF, Histamine...*)

- Pneumonia (*Infectious*)
- ARDS
- Sepsis
- Inhaled toxic agents
- Smoke inhalation
- Aspiration pneumonia
- Radiation pneumonia
- Drowning & near drowning
- Transfusion reaction
- Uremia

### C) Lymphatic insufficiency: Congenital & acquired

### D) $\downarrow\downarrow$ Oncotic pressure: Hypoalbuminemia

### E) $\uparrow\uparrow$ Negative interstitial pressure

- Upper airway obstruction
- Lung re-expansion

### F) Miscellaneous causes

- Neurogenic pulmonary edema
- High-altitude pulmonary edema
- Heroin pulmonary edema
- Pancreatitis
- Pulmonary embolism
- Eclampsia

## Clinical Picture (Clinical diagnosis)

- Variable degrees of RD
- Frothy sputum (Blood-tinged)
- Chest examination: Coarse crepitations (Bubbling)  $\pm$  Wheezes

## Investigations

- **CXR:** Haziness of both lung fields "butterfly pattern" (sparing the lung apices)
- **Brain natriuretic peptide:**  $\uparrow\uparrow$  in heart disease

## Treatment

- ICU
- Oxygen therapy
- Diuretics: Furosemide
- Aminophylline
- Morphine (Sedation & VD)
- Positive Inotropes...
- Mask or nasal CPAP
- Mechanical ventilation:  $\uparrow\uparrow$  PEEP
- Rx of the cause
- Dialysis (Non-renal...???)

	Cardiogenic	Non-Cardiogenic
Heart size	$\uparrow\uparrow$	Normal
Vascular pedicle	$\uparrow\uparrow$	Normal
Edema	Central	Patchy
Effusion	Present	No
Septal lines	Present	No
Air bronchogram	No	Present

# Community-Acquired Pneumonia

## Definition

- Inflammation of the lung parenchyma
- Recurrent pneumonia:  $\geq 2$  attacks in 1 year or  $\geq 3$  attacks ever

## Epidemiology

- 1<sup>st</sup> or 2<sup>nd</sup> cause of death in developing countries (19% of all < 5 yrs deaths)
- Incidence is 10 fold higher than developed countries
- Recently, there is  $\downarrow\downarrow$  in pneumonia mortality (Antibiotics, vaccines)
- There is  $\downarrow\downarrow$  in pneumonia caused by H.influenza, pneumococci & measles

## Pathology

- Alveoli: Consolidation
- Interstitium: Infiltration with inflammatory cells

## Classification

- A) **Anatomical:** Lobar, bronchopneumonia or interstitial pneumonia  
 B) **Etiological:** Infectious or noninfectious ...

## Etiology

- A) **Bacterial:**
- Gram +Ve: Streptococcus pneumoniae, Staphylococci, Streptococci
  - Gram -Ve: Hemophilus influenza, Klebsiella, Pseudomonas
  - TB, Mycoplasma
- B) **Viral:**
- Common:** RSV, adenoviruses, parainfluenza, influenza
  - Uncommon:** Rhinovirus, enterovirus, HSV, CMV, measles, varicella
- C) **Fungal:** Histoplasma, Aspergillus, Cryptococcus, Pneumocystis jirovecii
- D) **Parasitic:** Ascaris
- E) **Rickettsial**
- F) **Other causes (Non-infectious):**
- Aspiration pneumonia: Amniotic fluid, food, foreign body, hydrocarbons
  - Hypostatic pneumonia: Lying in one position for long time (lung congestion & edema)
  - Hypersensitivity
  - Radiation

Bacterial			
Common	Comment	Uncommon	Comment
Strept. pneumoniae	Consolidation, empyema	H. influenzae type b	Unimmunized
Group B streptococci	Neonates	Staph. aureus	Infants, pneumatoceles
Group A streptococci	Empyema	Moraxella catarrhalis	
Mycoplasma pneumonia*	Adolescents	Neisseria meningitidis	
Chlamydia pneumonia*	Adolescents	Francisella tularensis	
Chlamydia trachomatis	Infants	Nocardia species	
Mixed anaerobes	Aspiration pneumonia	Chlamydia psittaci*	
Gram-negative enterics		Yersinia pestis	Plague
		Legionella*	Contaminated water
		Coxiella burnetii*	Q fever

Streptococcus pneumoniae is the commonest bacteria in children 3 wks to 4 yrs

Mycoplasma & Chlamydia are the commonest > 5 yrs

S. pneumonia, H. influenza & S. aureus are the major causes of hospitalization & mortality

\*Atypical pneumonia: may have extrapulmonary manifestations, low-grade fever, -Ve sputum & ?Rx

## Clinical Picture

- History of preceding URT infection
- **Fever:** higher in bacterial causes (& chills)
- **Respiratory distress:** Tachypnea, retraction, grunting, cyanosis
- **Chest Examination:** ↓↓ Air entry, crepitations, wheezes
  - Inspection: RD
  - Palpation: TVF, position of the trachea
  - Percussion: Dullness with consolidation, collapse or effusion
  - Auscultation: ↓↓ Air entry, crepitations, wheezes

## Investigations

**NB:** Repeat CXR is not indicated to prove cure

- CBC, ESR, CRP
- Sputum culture
- Blood culture: positive in 10% of patients with pneumococcal pneumonia
- Nasopharyngeal aspirate: for viral agents (RSV)
- Pleural fluid examination
- Serology: paired samples with 14 days interval
- CXR
  - Bacterial: Lobar consolidation (air bronchogram)
  - Staph: Pneumatocele, abscess
  - Viral: Parahilar shadows with radiating streaks
  - Mycoplasma: Patchy segmental consolidation & hilar lymphadenopathy

## Causative organism

		Bacterial pneumonia	Viral pneumonia
Fever		High	Mild-moderate
Severity		More severe	Less severe
Lab.	CBC	Leukocytosis (PNLs)	Leukocytosis (Lymphocytes)
	CRP	Positive	Negative
	ESR	↑↑	Normal or mildly ↑↑

## Pathological types

	Lobar pneumonia	Bronchopneumonia	Interstitial pneumonia
Site	Unilateral affection of one or more lobes	Bilateral involvement of both lungs	Bilateral involvement of interstitial tissues
Etiology	Bacterial Mycoplasma	Bacterial Viral	Mostly viral
Chest Ex.	Auscultation: <ul style="list-style-type: none"> <li>▪ ↓↓ Air entry</li> <li>▪ Bronchial breathing</li> </ul>	Auscultation: <ul style="list-style-type: none"> <li>▪ Fine consonating crepitations</li> </ul>	Auscultation: <ul style="list-style-type: none"> <li>▪ Expiratory wheezes</li> </ul>
CXR	Lobar consolidation	Fine nodular or Patchy infiltration	Dense parahilar shadows with radiating streaks

## Treatment

### Indications of Hospitalization in children with pneumonia

1. Age < 6 months
2. Immunocompromised: 1ry, 2ry, sickle cell disease
3. Toxic appearance
4. Severe RD
5. Vomiting
6. Dehydration
7. Requirement for supplemental O<sub>2</sub> therapy (O<sub>2</sub> Saturation < 90% in room air)
8. Social factors: Non-compliance...

#### A) **Mild pneumonia in older children:** Home management

1. Close observation (Degree of RD)
2. Antibiotics

2mo-5y	≥ 5y
<b>-Oral Amoxicillin</b> 80mg/kg/day in 3 divided doses for at least 7 days <b>-Alternatives</b> <ul style="list-style-type: none"> <li>➤ Amoxicillin/Clavulinate</li> <li>➤ Oral cephalosporins</li> <li>➤ Macrolides</li> </ul> <b>-Consider 24 hours of a parenteral 3<sup>rd</sup> generation cephalosporin in patients with more severe disease:</b> <ul style="list-style-type: none"> <li>➤ Ceftriaxone 50 mg/Kg once, or</li> <li>➤ Cefotaxime 50-100 mg/Kg/day</li> </ul>	<b>Macrolides:</b> Erythromycin 40 mg/kg/day for ≥ 7 days or Azithromycin 10 mg/kg/day for 3-5 days

#### B) **Moderate to Severe pneumonia:** Hospital management

- a. Non specific support**
  1. Oxygen therapy
  2. Suction of airway secretions
  3. Physiotherapy
  4. Proper hydration: IV fluid
  5. Mechanical ventilation may be needed in severe cases
- b. Specific**
  1. Parental antibiotic therapy
  2. Antibiotics should be modified according to the results of culture & sensitivity

Neonates	1mo- 5 yrs	≥ 5y
I.V. Ampicillin (100 mg/Kg/day) +Gentamycin (5 mg/Kg/day)	Parenteral 3 <sup>rd</sup> generation cephalosporin	I.V. Ampicillin or Parenteral 3 <sup>rd</sup> generation cephalosporin + Macrolide
<b>Critically ill</b>		
Add 3 <sup>rd</sup> generation cephalosporin	Parenteral cephalosporin + Amoxicillin/ Clavulinate	Parenteral 3 <sup>rd</sup> generation cephalosporin + Macrolide

## Complications

1. Respiratory failure: Most serious
2. Pleural effusion: Bacteria specially Staphylococci & Streptococcus pneumoniae
3. Lung abscess: Bacteria specially Staphylococci
4. Pneumothorax: Bacteria specially Staphylococci & Klebsiella
5. Myocarditis & Acute HF: In infants with severe bacterial infection
6. Hematologic spread: Meningitis, arthritis, osteomyelitis...
7. Complications of mycoplasma
  - **Bacterial superinfection**
  - **CNS:**
    - Meningoencephalitis
    - Aseptic meningitis
    - GBS & transverse myelitis
    - Ataxia
  - **Hematological:**
    - AIHA (Cold hemagglutinins)
    - Thrombocytopenia
  - **Skin:**
    - Erythema multiforme
    - Stevens-Johnson syndrome
  - **Others:**
    - Hepatitis
    - Pancreatitis
    - Arthritis
    - Myocarditis & Pericarditis

## Prevention

### Important Remarks about some bacterial pneumonia

Organism	Comment
<b>Hemophilus influenza pneumonia</b>	Usually lobar Complications: meningitis (CSF?) Rx: Cefotaxime or ceftriaxone
<b>Staphylococcal pneumonia</b>	Usually bronchopneumonia Unilateral or more prominent on one side Complications: Cavitation, abscess formation, pneumatocele, pneumothorax, pleural effusion & empyema Rx: Amoxicillin-clavulanic acid Ampicillin-sulbactam Oxacillin Vancomycin or clindamycin
<b>Pneumococcal pneumonia</b>	Usually bronchopneumonia Complications: Pleural effusion & empyema Rx: Penicillin G
<b>Klebsiella pneumonia</b>	Usually bronchopneumonia Complications: As staphylococcal pneumonia

# Slowly resolving pneumonia

## Definition

- Persistence of symptoms or radiographic findings beyond the expected time course
- Typically, improvement of clinical symptoms occurs within 48-96 hrs after Rx

## Etiology

1. Complications: empyema
2. Bacterial resistance
3. Non-bacterial causes: TB & viruses
4. Noninfectious causes: Bronchiolitis obliterans, Wegener granulomatosis
5. Bronchial obstruction: Foreign body, mucous plugs...
6. Immunodeficiency
7. Lung disease: Immotile cilia syndrome, cystic fibrosis

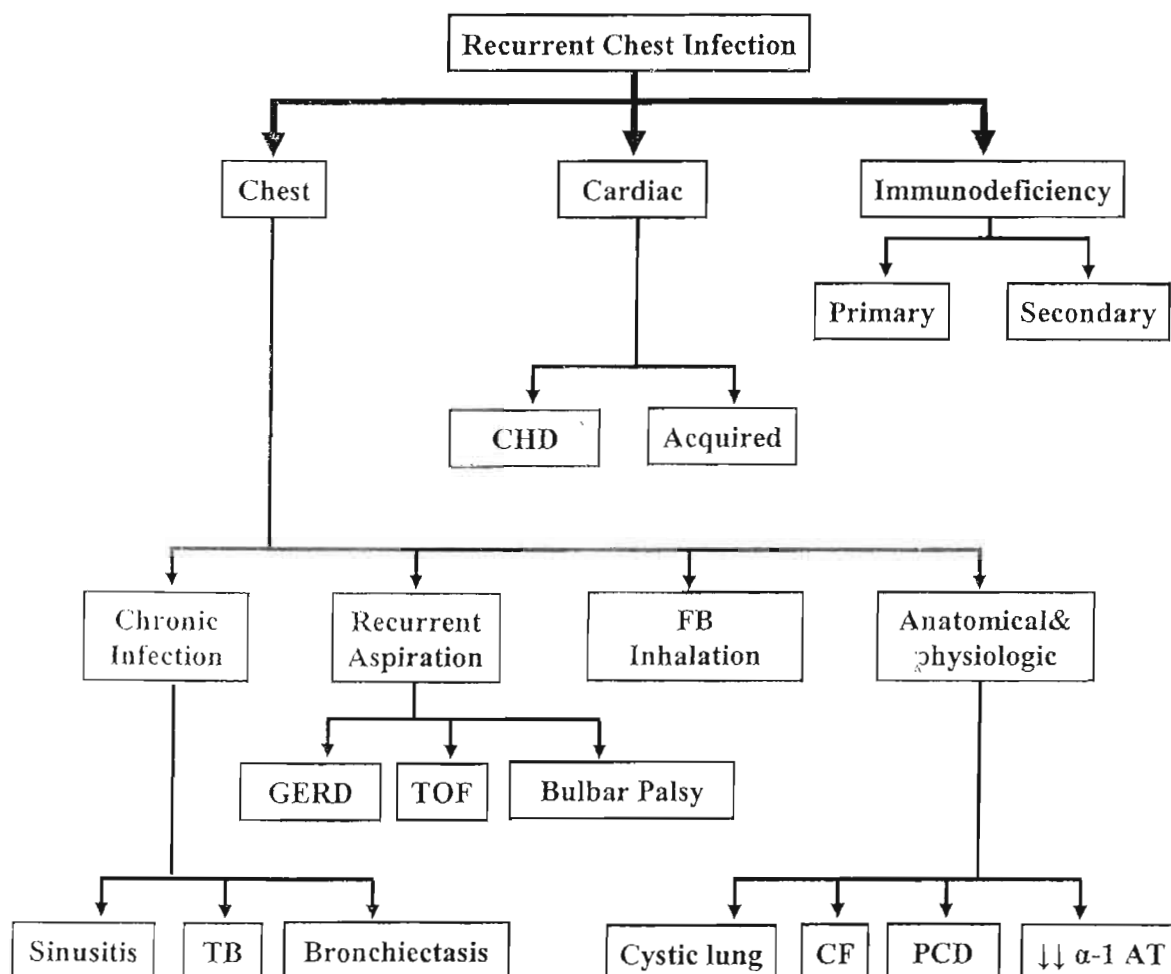
## Evaluation

- Repeat the CXR is the 1<sup>st</sup> step
- Investigations of the possible etiology: CT chest, bronchoscopy, ANCA...

# Recurrent Chest Infection

Normal RCI Up to 6-8 acute respiratory illnesses per year is not unusual?!

## Abnormally RCI



# Pneumonia

	Viral Pneumonia	Mycoplasma	Bacterial Pneumonia
Age	2-3 years	School-aged children	<ul style="list-style-type: none"> <li>- Infancy: Staphylococci</li> <li>- 2-5 yrs: Streptococci (Group A)</li> </ul>
Etiology	RSV, Parainfluenza, influenza, adenoviruses	Mycoplasma pneumoniae "The smallest self-replicating agents"	<ul style="list-style-type: none"> <li>- Streptococcus pneumoniae</li> <li>- Staphylococci</li> <li>- Streptococci</li> <li>- Hemophilus influenza type b</li> <li>- Chlamydia</li> </ul>
Pathology	Bronchopneumonia or interstitial	Bronchopneumonia or interstitial	Lobar or Bronchopneumonia
Symptoms	<ul style="list-style-type: none"> <li>▪ Preceding upper respiratory tract symptoms; cough &amp; rhinitis</li> <li>▪ Fever is &lt; bacterial pneumonia</li> <li>▪ Variable degrees of RD</li> </ul>	<ul style="list-style-type: none"> <li>▪ FAHM</li> <li>▪ Cough usually ↑↑ during the 1<sup>st</sup> week</li> <li>▪ Symptoms severity &gt; Physical signs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Preceding upper respiratory tract symptoms</li> <li>▪ Fever: High ± chills</li> <li>▪ Variable degrees of RD</li> </ul>
Chest signs			
Auscultation	Normal or scattered crepitations & wheezes	Crepitations	Localized bronchial breathing & crepitations
CXR	<ul style="list-style-type: none"> <li>- Bronchopneumonia or interstitial</li> <li>- Hilar lymphadenopathy</li> </ul>	<ul style="list-style-type: none"> <li>- Patchy segmental consolidation</li> <li>- Hilar lymphadenopathy</li> </ul>	<ul style="list-style-type: none"> <li>- Lobar consolidation</li> <li>- Bronchopneumonia</li> </ul>
CBC, CRP, ESR	<ul style="list-style-type: none"> <li>- Normal or mildly ↑↑ TLC</li> <li>- Lymphocyte predominance</li> </ul>	Normal TLC	<ul style="list-style-type: none"> <li>- Leukocytosis (↑↑ TLC)</li> <li>- PNLS predominance</li> </ul>
Other Investigations	<ul style="list-style-type: none"> <li>- Serology: IgM or rising IgG</li> <li>- Viral culture</li> <li>- Detection of viral antigens</li> </ul>	<ul style="list-style-type: none"> <li>- Serology: IgM or rising IgG</li> <li>- Sputum culture</li> <li>- Direct coombs' test &amp; reticulocytosis</li> </ul>	<ul style="list-style-type: none"> <li>- Sputum: Culture &amp; Sensitivity</li> <li>- Blood: Culture &amp; Sensitivity</li> <li>- Pleural tap: Cytology &amp; culture</li> </ul>
Treatment			
Medical Rx	<ul style="list-style-type: none"> <li>▪ Antibiotics are not indicated</li> <li>▪ Coexisting bacterial infection. in 50%</li> <li>▪ Ribavirin may be used in infants with CHD or chronic lung disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Macrolides: Erythromycin, Clarithromycin, Azithromycin</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mild cases: Amoxicillin (± clavulanic acid)</li> <li>▪ Severe cases: Parental Antibiotics; cephalosporins (Cefotaxime, ceftriaxone)</li> <li>▪ Staphylococci: Vancomycin or clindamycin</li> <li>▪ Modify antibiotics according to C &amp; S</li> </ul>
Surgical Rx			<ul style="list-style-type: none"> <li>▪ Intercostal tube drainage under water seal</li> </ul>
Complications			



# **Chronic Recurrent Aspiration**

## **Definition**

- Recurrent aspiration of gastric, nasal, oral secretion
- Wide clinical spectrum; asymptomatic to life-threatening events

## **Pathology**

- Granulomatous inflammation
- Interstitial inflammation & fibrosis

## **Effects of Aspiration**

- Cough, bronchitis & bronchiolitis
- Pneumonia, wheezes, atelectasis, laryngospasm



## **Predisposing Factors of Aspiration**

### **A) Anatomical**

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Micrognathia & Macroglossia | <input checked="" type="checkbox"/> N/G tube, ETT, tracheostomy |
| <input checked="" type="checkbox"/> Cleft palate                | <input checked="" type="checkbox"/> Achalasia                   |
| <input checked="" type="checkbox"/> Tracheoesophageal fistula   | <input checked="" type="checkbox"/> Scleroderma                 |
| <input checked="" type="checkbox"/> Vascular ring               | <input checked="" type="checkbox"/> GERD & hiatus hernia        |

### **B) Neuromuscular (Esophageal dysmotility)**

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> Cerebral palsy & Chiari malformation                          | <input checked="" type="checkbox"/> Myasthenia gravis    |
| <input checked="" type="checkbox"/> Stroke  | <input checked="" type="checkbox"/> Muscular dystrophies |
| <input checked="" type="checkbox"/> Multiple sclerosis  | <input checked="" type="checkbox"/> Polio, SMA           |
| <input checked="" type="checkbox"/> Cricopharyngeal achalasia: Failure of relaxation of UES       |  |
| <input checked="" type="checkbox"/> Cricopharyngeal incoordination: Incoordination of contraction |  |

### **C) Miscellaneous**

- ☒ Poor oral hygiene
- ☒ Poor feeding techniques: overfeeding, inappropriate foods...

## **Approach to a child with frequent aspiration**

## **Investigations**

- CXR: Infiltration, atelectasis
- HRCT chest
- Barium swallow: Useful in...
- Videofluoroscopic swallow study (VSS): Gold standard for evaluation of swallowing
- Esophageal pH monitoring
- MII
- Gastroesophageal scintigraphy
- Radionuclide salivagram
- Fiberoptic endoscopic evaluation of swallowing (FEES)
- Bronchoscopy (BAL): Lipid-laden macrophages

## **Treatment**

- Treatment of the cause
- Supportive Rx: Proper position, thickened foods, ↓↓ amount/feed, NG tube, postpyloric
- Medical Rx: Anticholinergic
- Surgical Rx: Fundoplication with gastrostomy tube, salivary gland excision

# **Pulmonary Hemosiderosis**

**(Diffuse alveolar hemorrhage = DAH)**

## **Definition**

- Triad of iron-deficiency anemia, hemoptysis & lung infiltrates (CXR)

## **Epidemiology**

- IPH: 1: 1 million

## **Etiology**

### **A) Primary hemosiderosis**

- Idiopathic pulmonary hemosiderosis (IPH)
- Goodpasture syndrome
- Heiner syndrome (Cow's milk allergy)

### **B) Secondary hemosiderosis**

- Congestive HF, mitral stenosis
- Pulmonary HTN, AVM, pulmonary VOD, pulmonary lymphangioleiomyomatosis
- Collagen-vascular diseases: SLE, HSP, APS, JRA, PAN, Wegener granulomatosis, microscopic polyangiitis
- Coagulopathy
- HUS, CRF, IgA nephropathy
- Immunodeficiency: CGD
- Drug-induced capillaritis
- Prematurity: immature alveoli & vessels
- Child abuse

### **Pulmonary hemosideosis:**

#### **a. With pulmonary capillaritis**

- Collagen-vascular
- Goodpasture syndrome
- Drug-induced capillaritis

#### **b. Without pulmonary capillaritis**

- Cardiac: HF, MS, pulmonary HTN
- Noncardiac: IPH, Heiner, ID

## **Pathology**

- Repeated episodes of pulmonary Hemorrhage
- Hemosiderin deposition  $\Rightarrow$  Hemosiderin-lade macrophages (HLMs)
- Hemosiderin is formed within 72 hrs & HLMs last for weeks after hemorrhagic event
- Inflammation (mediators) & neutrophil influx
- Thickening of alveolar septa & finally, pulmonary fibrosis

## **Clinical Picture** (Variable)

- Variable: Asymptomatic  $\longleftrightarrow$  Shock & sudden death
- Hemoptysis may not occur!!
- RD, cough, wheezes, why?
- General examination: Pallor, tachycardia, RD, fever, shock (severe hemoptysis)

## **Investigations**

- CBC: Microcytic hypochromic anemia, eosinophilia
- Retics & Bilirubin:  $\uparrow\uparrow$
- Iron studies:  $\downarrow\downarrow$  iron,  $\uparrow\uparrow$  TIBC
- ANA, Anti DNA, APA, ANCA, Anti-GBM
- Stools: Occult blood in stools
- Sputum & BAL: HLMs
- CXR: lung infiltrates "butterfly pattern" (sparing the lung apices)
- CT chest
- Pulmonary function tests: Obstructive changes (Late: restrictive)
- DLCO:  $\uparrow\uparrow$ , why?

**Treatment**

- **Supportive therapy:** Oxygen therapy, ventilator support, IVF, blood transfusion
- **IPH:** Steroids (2 mg/Kg/d) ± immunosuppressives
- **Lung transplantation**

**Pulmonary Hge & Hemoptysis****Definition**

- Pulmonary hemorrhage; hemoptysis may be absent

**Epidemiology** Underestimated, why?**Etiology****A) Focal hemorrhage**

- Infection: Bronchitis, bronchiectasis, CF
- TB
- Trauma: tracheostomy
- Tumors (Hemangioma)
- Pulmonary AV malformation
- Pulmonary embolism
- FB

**Focal hemorrhage can be treated by embolization or lobectomy**

**B) DAH: See before****C) Acute idiopathic pulmonary hemorrhage (AIPH):** In infants  $\leq 1$  yr**Atelectasis****Definition**

- Incomplete expansion or collapse of lung tissue with decreased aeration
- It may be segmental, lobar or complete lung collapse
- 90% affecting the upper lobes (Rt > Lt)

**Etiology**

Causes		Examples
External compression		Pleural effusion, pneumothorax, diaphragmatic hernia
Obstruction	Obstruction (Lumen)	FB, granulomatous tissue, mucous plugs, broncholithiasis, ETT
	Obstruction (Wall)	LN, stricture, bronchiolitis, asthma
	Obstruction (Outside)	LN, tumor, cardiomegaly, pulmonary abscess, vascular ring
Respiratory paralysis		Neuromuscular abnormalities, restrictive casts & dressings, osseous deformities, defective movement of the diaphragm

**Clinical Picture**

- Variable degrees of RD (asymptomatic if small)
- Chest examination: (Inspection...) Retraction, mediastinal shift, Dullness, ↓↓ air entry

**Investigations** CXR, CT, Bronchoscopy**Treatment** Respiratory support, physiotherapy, suction, DNase, CPAP

# Pneumothorax

## Definition

- It is the presence of air within the pleural space

## Incidence

- Asymptomatic pneumothorax affects up to 1-2% of all newborn infants

## Etiology

### A) Spontaneous

#### a. Primary:

- No trauma, No lung disease
- Reported in some families (Folliculin gene)

#### b. Secondary

- ☒ **Congenital lung diseases:** Lung hypoplasia, CCAM, CLE, bronchogenic cyst
- ☒ **Infections:** Pneumatocele, lung abscess
- ☒ **Conditions with ↑↑ intrathoracic pressure:** Asthma, bronchiolitis, CF, FB, MAS
- ☒ **Diffuse lung diseases:** Ehlers-Danlos, Marfan, Langerhans cell histiocytosis
- ☒ **Metastatic:** Osteosarcoma\*

### B) Traumatic

#### a. Non-iatrogenic: Blunt or penetrating injury

#### b. Iatrogenic

- **Barotrauma** (ambu-bag or mechanical ventilation)
- Vigorous resuscitation or physiotherapy
- Vascular access insertion "pleural injury"
- Chest surgery, tracheostomy, thoracocentesis

#### **Barotrauma:**

1. ↑↑ Pressure (PIP or PEEP)
2. ↑↑ IT
3. ↓↓ Expiratory time
4. ETT
5. Improved pathology without...
6. Unilateral lung pathology
7. Inadequate humidification
8. Aggressive physiotherapy

## Pathogenesis

- Hypoxemia (V/Q mismatch)
- Simple pneumothorax: Intrapleural pressure is atmospheric
- Tension pneumothorax: IPP is ↑↑ (Compression, shift, ↓↓ VR & CO, Obstructive shock)

## Clinical Picture

- Variable degrees of RD (asymptomatic if small)
- Chest examination: Inspection...
- Chest examination: Unilateral bulge, mediastinal shift, hyper-resonance, ↓↓ air entry
- May be bilateral in 10%
- Tension pneumothorax (↓↓ VR, ↓↓ BP): Obstructive shock

## Investigations

- CXR: Jet-black translucency + Mediastinal shift (may be absent, when?)
- Needle aspiration (2<sup>nd</sup> intercostals space MCL): "Diagnostic Therapeutic test"

## Treatment

- Conservative management (if asymptomatic): Observation + 100 % O<sub>2</sub>
- Needle aspiration
- Chest tube with underwater-seal drainage
- HFV is the ventilatory treatment of choice

## Complications

- Respiratory failure
- Obstructive shock
- SIADH
- ICH (↑↑ Intra-thoracic pressure)

# **Pulmonary Embolism & Infarction**

## **Incidence**

- 1: 100.000

## **Etiology (Risk Factors)**

1. **Environmental** Smoking, immotility
2. **Women's health:** OCPs, Pregnancy, hormonal replacement therapy
3. **Surgical**
  - Trauma
  - Orthopedic, neurosurgical & general surgery
4. **Thrombophilia:**
5. **Medical conditions**
  - DM, HTN, HF, obesity
  - Central venous catheter
  - Malignancy
  - Permanent pacemaker
  - Intracardiac defibrillator
6. **Non-thrombotic**
  - Air, Amniotic fluid, fat, bone, tumors, FB

## **Pathogenesis**

- V/Q mismatch (Dead space) & hypoxia
- Hyperventilation & hypocapnia
- Pulmonary infarction is unusual, why?
- Pulmonary HTN & cor pulmonale

## **Clinical Picture**

- Picture of the cause
- Variable presentation (may be asymptomatic)
- Pain, dyspnea, cough
- RVF
- Chest examination: localized crackles may be detected

## **Investigations**

- CXR: Non-specific
- Spiral CT angiography
- Pulmonary angiography
- EEG: RV strain
- Echo-:
- ABG: Hypoxia
- Lung scan
- Investigations of the cause

## **Treatment**

- Stabilization
- Anticoagulation: Heparin or LMW heparin followed by oral anticoagulant
- Thrombolytic therapy
- Surgical embolectomy

## **Prognosis**

- Mortality: 2.2%

# Parynchymal Diseases with prominent Hypersensitivity, Eosinophilic infiltration

## Hypersensitivity pneumonitis

(Extrinsic allergic alveolitis)

### Definition

- Immune-mediated diffuse inflammatory disease of the pulmonary interstitium caused by inhalation of organic antigens (typically animal or vegetable origin but may be drug-related)

### Etiology & Types of HP

- **Farmer's lung:** From moldy hay
- **Bird fancier "Breeder lung":** From the feces or urine of some bird & animal species
- **Ventilation "humidifier HP":** From contaminated humidifiers or air conditioners
- **Pigeon breeder disease**
- **Bagassosis:** Sugarcane
- **NB:** The usual antigen is thermophilic actinomycetes
- **NB:** Feather filled bedding (pillows, quilts) can cause the disease

### Pathogenesis

- **Acute:** Infiltration by PNLs, lymphocytes, plasma cells & macrophages
- **Subacute:** Noncaseating granuloma & bronchiolitis
- **Chronic:** Noncaseating granuloma, interstitial fibrosis & honeycombing
- **Mechanism:** Type III & IV hypersensitivity reactions

### Clinical Picture (High index of suspicion)

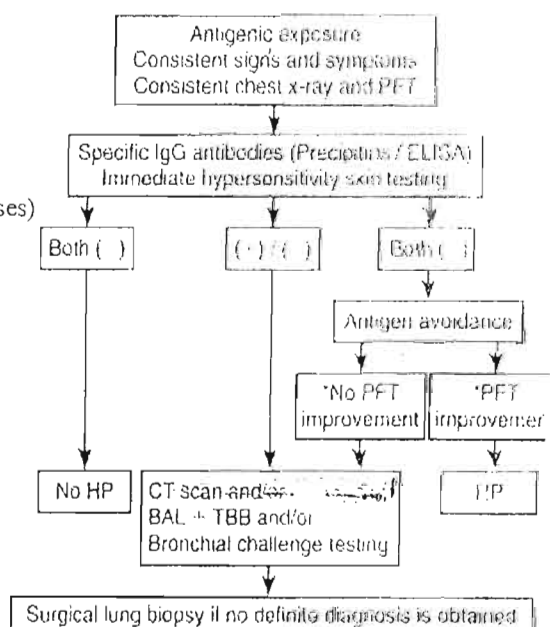
- **Acute (within 4-8 hr after exposure):** Fever, chills, cough, dyspnea, myalgia & malaise
- **Subacute:** Cough, dyspnea, anorexia & weight loss
- **Chronic:** Cough, dyspnea, anorexia, weight loss, hypoxemia, clubbing & cor pulmonale
- **Major criteria:** Compatible C/P, exposure (antibody studies), compatible CXR or HRCT, BAL (lymphocytes), compatible histology & positive antigen provocation challenge
- **Minor criteria:** Bibasilar crackles, ↓↓ diffusion capacity & hypoxemia

### Investigations

- CBC: leukocytosis, neutrophilia, shift to left
- Serum IgG, IgM & IgA: ↑↑
- Specific IgG antibody studies
- Skin testing to particular antigens
- Inhalational challenge: certain centers
- CXR: ground-glass haziness (sparing lung apices & bases) reticulonodular
- HRCT: may show bronchiectasis
- PFT: Restrictive pattern

### Treatment

- Avoidance
- Prednisone (1-2 mg/kg/24 hr) for 6-12 mo



## **Silo Filler Disease**

**(Silage gas poisoning)**

### **Definition**

- Lung disease caused by nitrogen dioxide toxicity which is produced in silos
- Dangerous concentrations of gas can remain in a closed silo for  $\approx 2$  wk

### **Pathogenesis**

- Inhalation, chemical pneumonitis, airway epithelial hyperplasia & pulmonary edema
- Methemoglobinemia in severe cases

### **Clinical Picture**

- Cough, dyspnea, wheezes
- Variable: Fatal, complete recovery, chronic lung disease (fibrosis & emphysema)

### **Investigations**

- CXR: Pulmonary edema

### **Treatment**

- High-dose prednisone
- Methemoglobinemia: Methylene blue

## **Paraquate Lung**

### **Definition**

- Paraquat is the most toxic dipyrilidium herbicide

### **Pathogenesis**

- Production of superoxides & free radicals leading to mitochondrial damage & cell death
- Paraquat-induced injury is increased in the presence of high  $O_2$  concentrations

### **Clinical Picture** (Dose-related)

- Asymptomatic
- Vomiting, diarrhea & caustic injury to the oral or esophageal mucosa
- Organ failure: Renal failure, hepatic dysfunction, pulmonary fibrosis, respiratory failure

### **Investigations**

- Plasma paraquat concentration (paraquat nomograms): Diagnostic & prognostic
- Urine dithionite test (turns urine blue if paraquat is present)

### **Treatment**

- Supportive
- Antioxidant therapy: Deferoxamine & acetylcysteine
- Immunosuppressive therapy consisting of IV steroids & cyclophosphamide
- Lung transplantation: Poor outcome, why?

### **Prognosis**

- Poor

# **Eosinophilic lung Disease**

**(Pulmonary infiltrates with eosinophilia (PIE) or Löffler Syndrome)**

## **Definition**

- Heterogenous group of disorders characterized by pulmonary infiltrates & circulating or tissue eosinophilia

## **Epidemiology**

- Rare in children (Only 6% of cases occurred in patients <20 yr of age)

## **Etiology**

### **A) Primary (Idiopathic)**

- ☒ Simple pulmonary eosinophilia (Löffler syndrome)
- ☒ Acute eosinophilic pneumonia
- ☒ Chronic eosinophilic pneumonia
- ☒ Idiopathic hypereosinophilic syndrome

### **B) Secondary**

- ☒ Tropical pulmonary eosinophilia
- ☒ Pulmonary eosinophilia with asthma
- ☒ Polyarteritis nodosa
- ☒ Churg-Strauss syndrome
- ☒ Allergic bronchopulmonary aspergillosis (ABPA)
- ☒ Drug-induced eosinophilic lung disease

## **Pathogenesis**

- The most common **etiologies** of PIE syndromes are parasite infections and drug reactions
- **Parasites:** *Ascaris lumbricoides*, *Strongyloides*, *Toxocara canis*, *Wuchereria bancrofti*
- **Drugs:** Sulfasalazine, penicillin, ampicillin, ibuprofen & cromolyn
- **Pathology:** Alveolar macrophages, lymphocytes, neutrophils & eosinophils

## **Clinical Picture**

- Cough, dyspnea, wheezes, malaise, fever
- In acute eosinophilic pneumonia, symptoms last for < 1 month
- In chronic eosinophilic pneumonia, symptoms last for > 6 months

## **Investigations**

- CBC: Eosinophilia
- CXR: Bilateral & diffuse nonspecific interstitial, alveolar, or mixed infiltrates  
[NB: Chronic eosinophilic pneumonia: photographic negative of pulmonary edema]
- BAL: Eosinophilia
- Lung biopsy

## **Treatment**

- Avoidance of exposure
- Rx of parasitic infestations
- Acute & chronic eosinophilic pneumonia: prednisone

## **Prognosis**

- Generally good
- Acute eosinophilic pneumonia may be fatal



# Interstitial Lung Diseases

## Definition

- Heterogenous group of disorders affecting the interstitium (the tissue around the alveoli)
- It involves alveolar epithelium, pulmonary capillary endothelium & basement membrane
- Some cases are familial (surfactant dysfunction disorders)

## Epidemiology

- Rare in children

## Etiology

### A) Disorders more common in infants

- ☒ Developmental disorders: acinar dysplasia, congenital alveolar dysplasia, alveolar capillary dysplasia
- ☒ Growth disorders (deficient alveolarization): Pulmonary hypoplasia, CHD, chromosomal disorders
- ☒ Surfactant dysfunction: SP-B mutation, SP-C mutation, ABCA3 mutation
- ☒ Pulmonary interstitial glycogenosis
- ☒ Neuroendocrine cell hyperplasia of infancy

### B) Disorders of known association

- ☒ Hypersensitivity pneumonitis
- ☒ Aspiration syndromes
- ☒ Infections: adenoviruses, influenza viruses, Chlamydia, Mycoplasma

### C) Disorders of immunocompromised host

- ☒ Opportunistic infections
- ☒ Therapeutic interventions: chemotherapy, radiation, transplantation

### D) ILD of unknown etiology

- ☒ Usual interstitial pneumonitis (UIP)
- ☒ Desquamative interstitial pneumonitis (DIP)
- ☒ Lymphocytic interstitial pneumonitis (LIP)
- ☒ Nonspecific interstitial pneumonitis (cellular/fibrotic)
- ☒ Eosinophilic pneumonia
- ☒ Pulmonary hemosiderosis
- ☒ Pulmonary alveolar proteinosis
- ☒ Pulmonary vascular disorders
- ☒ Pulmonary lymphatic disorders
- ☒ Pulmonary microlithiasis

### E) Systemic disorders with pulmonary involvement

- ☒ Collagen-vascular disorders
- ☒ Malignancies
- ☒ Langerhans cell histiocytosis
- ☒ Sarcoidosis
- ☒ Neurocutaneous syndromes: NF & TS
- ☒ Storage diseases: Gaucher & Niemann-Pick
- ☒ Vasculitis: Wegener & Churge-Strauss syndrome

## Clinical Picture

- Symptoms are usually insidious and continuous (Not episodic)
- Cough, dyspnea, FTT, clubbing, cyanosis (Wheezing and fever are **not** common)
- Hypoxemia (Hypercarbia is late, why?)
- Late: pulmonary HTN, cor pulmonale
- Picture of the cause: pulmonary hemosiderosis...

## **Investigations**

- CXR & CT chest: interstitial, reticular, nodular, reticulonodular, or honeycombed
- HRCT chest: Better information
- PFTs: restrictive pattern
- BAL: Pulmonary alveolar proteinosis & pulmonary hemosiderosis
- Lung biopsy

## **Treatment**

- Supportive care: O<sub>2</sub> therapy (hypoxia), adequate nutrition, antimicrobial Rx (infections)
- Some cases may respond to bronchodilators
- Corticosteroids: treatment of choice (*1-2 mg/kg/24 hr for 6-8 wk with gradual tapering*)
- Other lines: Azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, MTX, IVIG, GM-CSF & pulse high-dose steroids
- Lung transplantation

## **Prognosis**

- Some children recover spontaneously, but others progress to death
- Pulmonary HTN, FTT & severe fibrosis are poor prognostic indicators

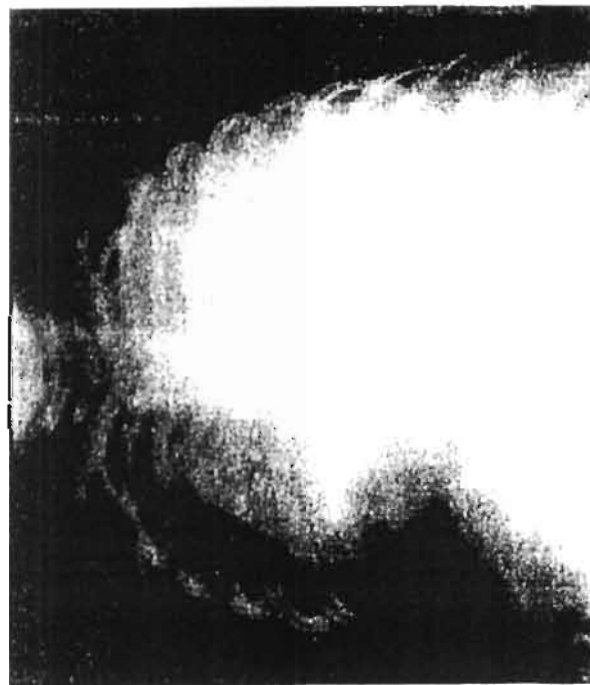
## Suppurative Lung Syndromes

### Definition

- Group of diseases characterized by suppurative inflammation of the pleura, lung or bronchi

	<b>Empyema</b>	<b>Lung abscess</b>	<b>Bronchiectasis</b>
<b>Definition</b>	Accumulation of pus in the pleural cavity	Localized suppurative inflammation resulting in a cavity containing pus	Permanent dilatation of the bronchi with suppurative inflammation of their walls
<b>Etiology</b>	<ul style="list-style-type: none"> <li>Bacterial pneumonia (Staph., Streptococcus pneumoniae, H. influenza)</li> <li>Trauma</li> <li>Mediastinitis</li> <li>Intra-abdominal abscess</li> </ul>	<ul style="list-style-type: none"> <li>Bacterial pneumonia (Staph., Klebsiella)</li> <li>Aspiration of infected material</li> <li>FB</li> <li>Metastatic lung abscess (Rt sided infective endocarditis)</li> <li>Amebic liver abscess</li> </ul>	<p>A) Congenital:</p> <ul style="list-style-type: none"> <li>Abnormal bronchial development</li> </ul> <p>B) Acquired: Chronic pulmonary infection</p> <ul style="list-style-type: none"> <li>Immunodeficiency</li> <li>Cystic fibrosis</li> <li>Immotile cilia syndrome</li> <li>Asthma</li> <li>Aspiration: FB, TOF, GERD</li> </ul>
<b>Pathology</b>	<ul style="list-style-type: none"> <li>Pleura: Inflammation</li> <li>Pleural space: Pus</li> </ul>	<ul style="list-style-type: none"> <li>Cavity containing pus</li> <li>Fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>Site: Usually bilateral &amp; basal</li> <li>Types: Cylindrical, sacular or fusiform</li> <li>Mucosa: Ulceration + loss of ciliated epith.</li> <li>Bronchial wall: Infiltration, edema, fibrosis</li> <li>Lumen: Mucus, pus ± blood</li> </ul>
<b>Symptoms</b>	<ul style="list-style-type: none"> <li>Fever, weight loss</li> <li>Cough, dyspnea</li> <li>Lying on the affected side</li> <li>Pain</li> </ul>	<ul style="list-style-type: none"> <li>FAHM, weight loss</li> <li>Cough, hemoptysis</li> <li>Expectoration of amount of purulent sputum followed by</li> <li>Marked relief of symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FAHM, weight loss</li> <li>Cough, dyspnea, expectoration of <b>excessive</b> amount of muco-purulent sputum (Changing with posture)</li> <li>Hemoptysis, RD, clubbing</li> </ul>
<b>Chest signs</b>			
<b>Inspection</b>	Unilateral bulge	Normal	Normal
<b>Palpation</b>	↓↓ Respiratory movement		
<b>Percussion</b>	Trachea & heart may be shifted to the opposite side	Central mediastinum ( Trachea & heart)	Central mediastinum (Trachea & heart)
	Stony dullness (on the affected side)	Localized dullness	Patchy dullness
<b>Auscultation</b>	↓↓ Air entry (on the affected side)	Localized bronchial breathing	Localized bronchial breathing & crepitations

<b>Investigations</b>			
<b>CXR</b>	<ul style="list-style-type: none"> <li>- Homogenous opacity obliterating C/P angle &amp; rising to the axilla</li> <li>- Mediastinal shift (Heart &amp; Trachea)</li> </ul>	<ul style="list-style-type: none"> <li>- Cavity ± Air-fluid level</li> <li>- No mediastinal shift (DD: Hydropneum.)</li> </ul>	<ul style="list-style-type: none"> <li>- Patchy areas of consolidation</li> <li>- Honey-comb appearance (Dilated bronchi)</li> </ul>
<b>Other Investigations</b>	CBC, ESR, CRP Thoracentesis: Culture & Sensitivity	CBC, ESR, CRP Sputum: Culture & Sensitivity	CBC, ESR, CRP Sputum: Culture & Sensitivity HRCT, bronchography, bronchoscopy
<b>Treatment</b>			
<b>Medical Rx</b>	<ul style="list-style-type: none"> <li>Antibiotics: according to C &amp; S</li> </ul>	<ul style="list-style-type: none"> <li>Antibiotics: according to C &amp; S</li> </ul>	<ul style="list-style-type: none"> <li>Antibiotics: according to C &amp; S</li> <li>Postural drainage &amp; physiotherapy</li> <li>Supportive: Expectorants &amp; mucolytics</li> </ul>
<b>Surgical Rx</b>	<ul style="list-style-type: none"> <li>Intercostal tube drainage under water seal</li> <li>Fibrinolytic agent (for the mass)</li> <li>VATS</li> <li>Open decortication</li> </ul>	<ul style="list-style-type: none"> <li>Bronchoscopy: Removal of FB</li> <li>Lobectomy: indicated if there is recurrent hemoptysis or resistant recurrent infection</li> </ul>	<ul style="list-style-type: none"> <li>Lobectomy: if localized</li> </ul>



Pleural effusion



Lt upper lobe lung abscess

# Bronchiectasis

## Definition

- Permanent dilatation of the bronchi with suppurative inflammation of their walls

## Epidemiology

- Incidence is decreasing in developed countries
- Male : female ratio is 2 : 1

## Etiology

### A) Congenital:

- **Williams-Campbell syndrome:** Absence of annular bronchial cartilage
- **Marnier-Kuhn syndrome** (congenital tracheobronchomegaly): CT disorder Primary

### B) Acquired: Gradually progressive

- Cystic fibrosis is the most common cause
- Primary ciliary dyskinesia
- Foreign body inhalation
- Aspiration of gastric contents
- Immune deficiency syndromes (especially humoral immunity)
- Infection: Pertussis, measles, rubella, RSV, TB
- **Rt middle lobe syndrome:** Compression of Rt middle lobe bronchus by hilar LN

## Pathogenesis & Pathology

- Mechanism: Obstruction + Infection + Inflammation
- Site: Usually bilateral & basal
- Types: Cylindrical, varicose (Dilatation with local constrictions), saccular (cystic) or fusiform
- Mucosa: Ulceration + loss of ciliated epithelium
- Bronchial wall: Infiltration, edema, fibrosis
- Lumen: Mucus, pus ± blood

## Clinical Picture

- FAHM, weight loss
- Cough, dyspnea, expectoration of ↑↑ amount of muco-purulent sputum (Postural)
- Hemoptysis, clubbing

## Investigations

- Culture: deep throat, sputum or BAL fluid
- CXR & CT chest: Nonspecific
- Thin-section HRCT: "Gold standard" ⇒
- Investigation of the cause: sweat Cl test



## Treatment

- **Medical:** Chest-physiotherapy (postural drainage), antibiotics & bronchodilators
- Long-term prophylactic: Oral (macrolide) or nebulized antibiotics
- **Surgical (Lobectomy):** Localized resistant bronchiectasis
- Lung transplantation

# Pulmonary Abscess

## Definition

- Localized suppurative inflammation (Cavity containing pus)

## Classification

- **Primary lung abscess:** occurs in a previously healthy patient (Rt\*)
- **Secondary lung abscess:** with underlying or predisposing conditions (Lt\*)

## Etiology

### A) Organisms:

- Anaerobic bacteria: Bacteroides, Fusobacterium, Peptostreptococcus
- Aerobic bacteria: Streptococcus, Staph. aureus, E. coli, Klebsiella, Pseudomonas
- Combined viral-bacterial infection
- Fungi: in immunocompromised patient

### B) Predisposing factors:

- Aspiration: GERD, TOF, neurologic diseases, seizures
- Foreign body inhalation
- Postoperative complications of adeno-tonsillectomy
- Pneumonia
- Cystic fibrosis
- Immunodeficiency

## Clinical Picture

- FAHM, weight loss
- Cough, dyspnea, hemoptysis
- Expectoration of ↑↑ amount of -purulent sputum followed by marked relief of symptoms

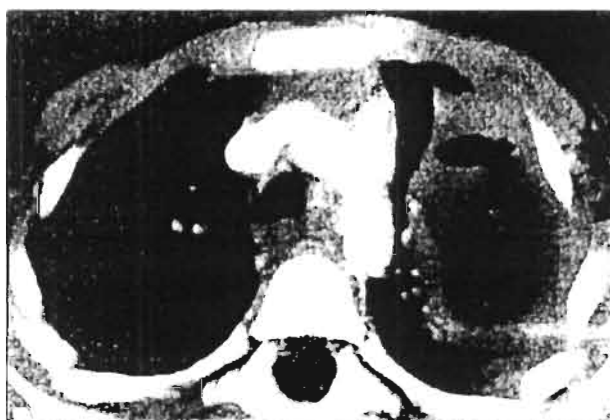
## Investigations

- Culture: Sputum (usually contaminated), BAL fluid, direct lung puncture, percutaneous or transtracheal aspiration
- CXR & CT: Thick-walled cavity with air-fluid level (DD: Pneumatocele; thin-walled)

## Treatment (Conservative management is recommended)

- **Antibiotics (4-6 wks):**
  - Parenteral for 2-3 wk, followed by oral antibiotics
  - Choice: Anti-Staph & anaerobic (Clindamycin)
- **Surgical:**
  - Indication: failure to improve after 7-10 days of appropriate antimicrobial therapy
  - Options: CT guided percutaneous aspiration, thoracotomy, lobectomy, decortication

**Empiric therapy can be initiated in the absence of culturable material**



# **Dry Pleurisy**

**Definition** Inflammation of the pleura

## **Etiology**

### **1. Infections**

- **Viral:** Coxsackievirus B, Adenovirus
- **Bacterial:** Streptococci, Staphylococci, Pneumococci, Meningococci & Mycoplasma
- TB

### **2. Collagen-Vascular**

- JRA
- SLE
- Scleroderma
- Rheumatic fever
- Vasculitis Syndromes
- Sarcoidosis

### **3. Familial Mediterranean Fever**

### **4. Traumatic**

### **5. Tumors:** Primary or metastases

### **6. Post-pericariotomy syndrome**

### **7. Metabolic:** Uremia, hypothyroidism

## **Clinical Picture**

- Pain: Stitching, localized ↑↑ with breathing & coughing and referred to the shoulder
- Position: lying on the affected side
- Pleural rub
- Other manifestations: FAHM, cough, dyspnea

**Investigations** CXR: Normal or may show small amount of pleural effusion

**Treatment** Analgesics: NSAIDs

# **Pleural Effusion**

**Definition** Accumulation of fluid in the pleural space

## **Etiology**

A) **Pleural exudate:** *The same causes...*

B) **Hydrothorax (Transudate)**

- Cardiac (HF), Renal (NS), Hepatic (LCF), Nutritional, Hypoalbuminemia
- Vascular obstruction (SVC)

C) **Hemothorax**

- Trauma
- Tumors
- TB
- VA insertion
- Pulmonary AV fistula
- Bleeding tendency

D) **Chylothorax**

E) **Empyema**

## **Clinical Picture**

- Pain: Dull
- Position: lying on the affected side
- Other manifestations: FAHM, cough, dyspnea
- Examination: Bulge, shift, dullness, ↓↓ air entry

## Investigations

- CXR & US: Pleural effusion...
- **Thoacocentesis:** Obtaining fluid from the pleural cavity  
Needle puncture should be along the upper border of the rib, why?  
Complications: Infection, bleeding, pneumothorax, liver/spleen injury

### **Pleural fluid examination** (Physical, Chemical, Cytological & Bacteriological)

- Physical: Clear in transudate, turbid in others
- Cytological: ↑↑ PNLs (Exudate), ↑↑ Lymphocytes (TB), Malignant cells
- Chemical: Milky fluid with ↑↑ TAG (Chylous), blood-stained (Tumors)
- Bacteriological: Culture

	Transudate	Exudate
Aspect	Clear	Turbid
Specific gravity	Low (< 1015)	High (> 1015)
Proteins	Low (< 2.5 g/dl)	High (> 2.5 g/dl )
Cell Number	Few (< 2000 /mm <sup>3</sup> )	Many (> 2000 /mm <sup>3</sup> )
Cell Type	Lymphocytes	PNLs
LDH	Low (< 200 IU/L)	High (> 200 IU/L )
pH	7.4-7.6	< 7.2
Pleural/Serum protein ratio	< 0.5	> 0.5
Pleural/Serum LDH ratio	< 0.6	> 0.6

## Treatment

- Rx of the cause
- Chest tube: Under water seal

# Chylothorax

**Definition** Accumulation of chyle in the pleural space

## Etiology

1. **Thoracic duct injury:** Cardiothoracic surgery, chest trauma, neonate (during delivery)
2. **Tumors:** Primary or metastases
3. **Congenital anomalies of lymphatics**
4. **Vascular obstruction** (SVC)
5. **Idiopathic**

## Investigations

- CXR
- Thoacocentesis (Milky fluid, may be clear, when?), fluid/serum TAG ratio > 1
- Lymphangiogram & lymphoscintigraphy

## Treatment

- Low-fat diet, MCT or TPN
- **Chest tube:** Under water seal
- Octreotide
- Surgical: thoracic duct ligation, pleuroperitoneal shunt...



# Pulmonary Tuberculosis

## Definition

It is a serious respiratory disease with a mortality rate of 8:100.000 (Egypt)

## Etiology

- a. Mycobacterium tuberculosis
- b. Mycobacterium bovis
- c. Mycobacterium africanum

### TB Bacilli:

- Aerobic
- Acid-fast bacilli
- Intracellular
- Stained by Ziel-Neelsen stain
- Culture: Lowenstein-Jensen medium

## Mode of transmission

- a. Inhalation: Droplet from patient with open TB
- b. Ingestion: Contaminated milk
- c. Inoculation: Skin contact

## Pathology (Direct tissue invasion)

1. Tubercle: Caseating granuloma
2. Exudative reaction: Effusion, ascites...

## Types & Pathogenesis of TB

### 1. Primary

- TB infection for the first time
- It occurs in one of 4 sites: Lungs, tonsils, intestine or skin
- Lung is the commonest site to be involved
- Leading to the formation of 1ry complex [Focus, TB lymphangitis, TB lymphadenitis]
- Fate of the 1ry complex:
  - Good immunity: Healing → Fibrosis ± Calcification
  - Poor immunity: Active 1ry disease ± Spread

### 2. Secondary

- a. Exogenous: Reinfection (Environmental)
- b. Endogenous: Reactivation (TB bacilli that have survived in the 1ry complex)

## Primary Pulmonary TB

### Etiology

### Mode of transmission

### 1ry complex

1. Ghon's Focus: Subpleural, 1-2 cm, usually in the lower part of the upper lobe or upper part of the lower lobe
2. TB lymphangitis
3. TB lymphadenitis (Hilar LN)

### Fate of the 1ry complex

1. Good immunity: Healing → Fibrosis ± calcification (Asymptomatic but reactivation...)
2. Poor immunity: Active 1ry disease ± Spread
  - Direct: Pneumonia, cavitation, pleurisy, pleural effusion
  - Bronchial: Larynx, pharynx, tongue, intestine
  - Blood: Isolated organ or miliary TB
  - LN enlargement: Pressure manifestations
    - Mediastinal structures: Mediastinal syndrome
    - Bronchi: Lung collapse or emphysema

## Clinical Picture

### A) Symptoms

- Contact with affected family member
- General (TB toxemia): Night fever, night sweat, anorexia, loss of weight
- Chronic cough: is the main symptom with or without expectoration
- Sputum may be mucoid, purulent or bloody sputum
- Chest pain, dyspnea or wheezes may occur
- Any chest symptom with **poor or no response to routine treatment**

### B) Signs

- Pneumonia: Signs of consolidation (↓↓ Air entry, bronchial breathing, crepitations)
- Effusion: Stony dullness, ↓↓ Air entry
- Fibrosis: Mediastinal shift to the SAME side (Heart & trachea)
- RD (variable grades 1-4)

## Investigations

### A) Laboratory

- CBC: Lymphocytosis
- ESR: Markedly ↑↑
- CRP: Positive

### B) Imaging

- CXR
- CT chest

### C) Bacteriological

- Sample: Sputum, stomach wash, gastric aspirate
- Direct smear: Ziel-Neelsen stain for acid fast bacilli
- Culture: Lowenstein-Jensen medium (requires 3-6 wks to give results)

### D) Biopsy

- Sample: LN, pleura, bronchoscopy...
- Pathology: Caseating granuloma

### E) Recent methods of diagnosis

- PCR (Polymerase chain reaction)
- ELISA (Enzyme-Linked Immuno-Sorbent Assay)
- BACTEC method: requires 1-3 wks

### F) Tuberculin test

- Principle: Delayed hypersensitivity reaction (Type IV) to TB bacilli
- Method: Mantoux test
  - Intra-dermal injection of 0.1 ml containing 5 units of purified protein derivative (PPD) in the skin of the flexor surface of the forearm
  - Area of induration (Not erythema) is measured 48-72 hrs after administration
  - Both longitudinal & transverse diameters are measured (The mean is recorded)
- Interpretation
  - < 5 mm: Negative
  - 5-9 mm: Doubtful (Repeated)
  - > 10 mm: Positive

Positive reaction	False negative reaction
▪ BCG vaccination (usually < 10 mm)	▪ SC administration or Outdated reagent
▪ TB infection	▪ Use of steroids or immunosuppressives
	▪ Cell-mediated immunodeficiency
	▪ Severe malnutrition & cachexia
	▪ Viral vaccines (Measles & mumps)
	▪ Viral infections (Measles & mumps)
	▪ Severe disseminated TB, hypothyroidism

## Prevention

### A) General measures

- Socioeconomic development & environmental sanitation
- Good housing, proper ventilation & spacing
- Health education
- Proper nutrition
- Food sanitation: Milk sanitation (Pasteurization)
- Regular health appraisal
- Mass radiography centers for early detection of affected individuals
- Diagnosis & Rx of those employed in the care of children in nurseries & schools

### B) Specific measures

#### a. BCG Vaccine [Bacillus-Calmette-Guerin]

- **Nature:** Live attenuated
- **Dose:** 0.1 ml (0.05 ml in neonates)
- **Route:** Intradermal in the Lt deltoid area
- **Timing:** Starting at birth (1<sup>st</sup> 3 months of life), Booster doses at 5 & 11 yrs
- **Contraindications:** Immunodeficiency, immunosuppressives
- **Precautions:** Tuberculin test is indicated if vaccination is delayed beyond 1<sup>st</sup> yr  
[Only tuberculin-negative individuals are vaccinated]
- **Advantages**
  - Prevention of pulmonary TB ( $\approx$  50% effectiveness)
  - Prevention of TB meningitis & disseminated disease ( $\approx$  50-80% effectiveness)
- **Side effects (Reaction):**
  - Erythema, papule formation  $\pm$  ulceration in 3-6 wks
  - Scar formation within 2-6 months
  - Regional lymphadenitis: Anti-TB treatment may be needed
  - Disseminated BCG infections: in immunocompromised individuals

#### b. Chemoprophylaxis

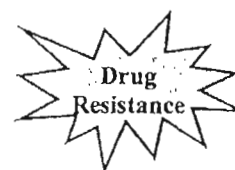
- **Indications:** High-risk close contacts
- **Dose:** Isoniazide (INH) 15 mg/Kg/day for 1 year

## Treatment

### A) Antituberculous drugs: Combined therapy (2-3 drugs 1<sup>st</sup> line drugs) for 6-9 months.

Combined therapy is preferred to minimize drug toxicity & development of drug resistance

First Line Drugs	Dose	Route
Isoniazide (INH)	10-15 mg/Kg/day	Oral
Rifampicin (RIF)	10-20 mg/Kg/day	Oral
Pyrazinamide (PZA)	20-40 mg/Kg/day	Oral
Alternative Drugs		
Streptomycin	20-40 mg/Kg/day	IM
Ethambutol	15-20 mg/Kg/day	Oral
Ethionamide	15-20 mg/Kg/day	Oral
Other drugs	Amikacin, Kanamycin, Para-aminosalicylic acid	



### B) Steroids may be given, when??

- TB serositis
- TB meningitis
- Miliary TB
- TB of the adrenal gland (Replacement therapy)
- Allergy to anti-TB drugs
- After removal of TB cervical LN to avoid fibrosis
- After removal of TB bronchial LN to avoid stricture

## **Extrapulmonary TB**

### **A) TB Lymphadenitis**

- Cervical LN are the most commonly involved
- Early: Firm, discrete, mobile, non-tender
- Late: Adherent & matted

### **B) Abdominal TB**

#### **a. TB enteritis**

- Chronic diarrhea, tenesmus, bleeding
- Stools: Whitish & greasy

#### **b. TB peritonitis**

- Ascitic type: Ascites with ↑↑ protein content & ↑↑ cells (mainly lymphocytes)
- Caseous type: Doughy sensation of the abdomen
- Adhesive type: Intestinal loops are glued together by fibrinous adhesions
- Encysted type: Small collections of ascetic fluid between adherent intestinal loops

#### **c. TB mesenteric lymphadenitis (= Tabes mesenterica)**

- Enlarged matted mesenteric LN palpable in the Rt iliac fossa with doughy sensation

#### **d. Urogenital TB**

- Renal TB results from hematogenous spread
- Affection of renal pelvis, ureters, bladder, prostate, seminal vesicles may follow
- Urine: Sterile pyuria (Culture may reveal TB bacilli)

### **C) CNS TB**

#### **a. TB meningitis**

- See before (↑↑ ICP, Irritability, Convulsions...)
- CSF: ↑↑ Protein, ↑↑ cells (mainly lymphocytes), ↓↓ Glucose, ↓↓ Chloride

#### **b. Tuberculoma**

- Formation of large caseous lesion
- Space-occupying manifestations

### **D) Skeletal TB**

#### **a. Pott's disease of the spine**

- Site: Lower thoracic (*Commonest site*), Lumbar, Cervical
- Nature: Destruction of vertebral bones
- C/P: Angular kyphosis (Not correctable)
- X-rays: Bone rarefaction & destruction

#### **b. TB arthritis**

- Site: Hip, Ankle, Knee, Elbow joints
- Nature: Inflammation of the joint
- C/P: Pain, swelling, limitation of movements
- X-rays: Bone rarefaction & destruction

### **E) Other types**

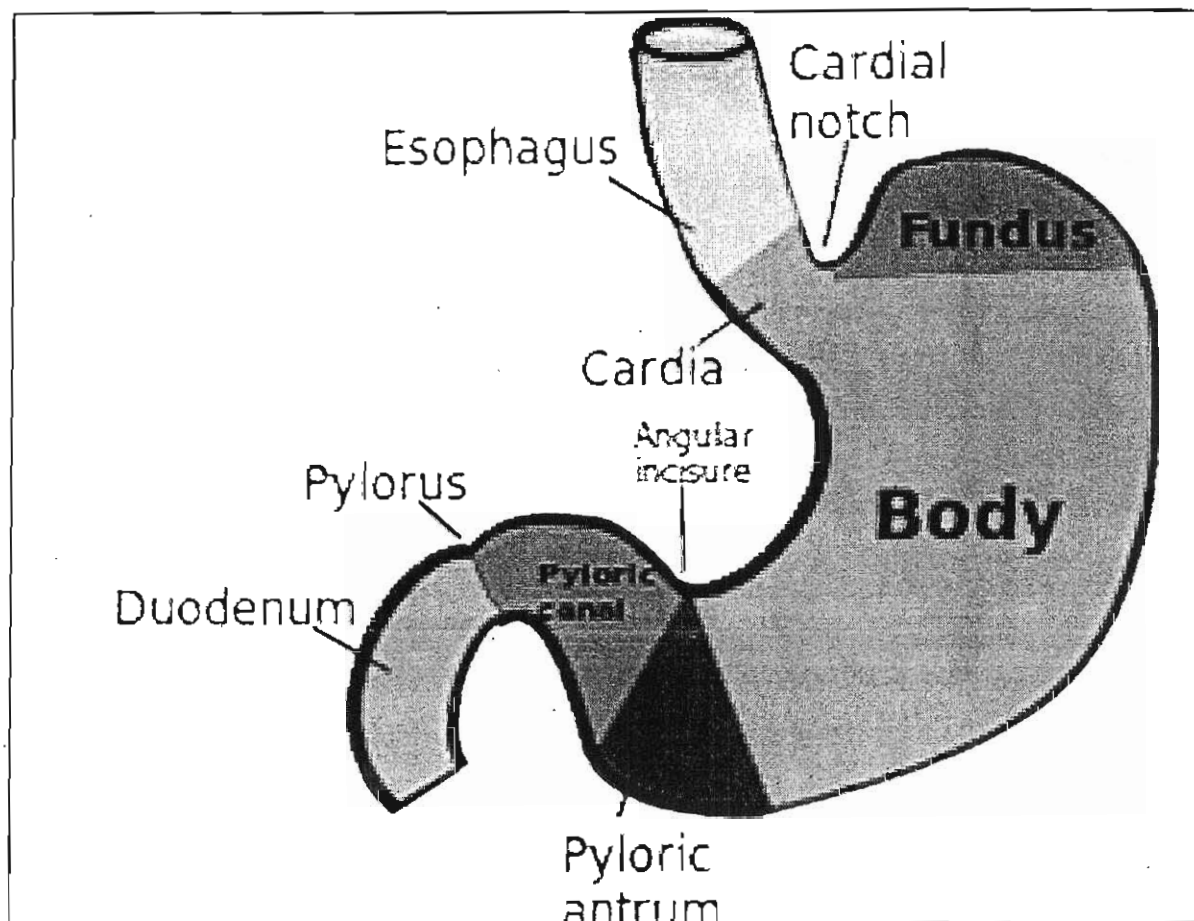
#### **a. TB pericarditis**

- Route: Lymphatic spread
- Types (Pathology): Serous & Constrictive
- Diagnosis: Pain, CXR, ECHO

#### **b. TB skin**

- Site: Chin, lips, nose, limbs, genitalia (Lupus vulgaris)

#### **c. TB of eye & ear: Conjunctivitis, chronic otitis media, mastoiditis**



# **Pediatric Gastroenterology**

*(For Master Degree)*

By

**Ahmed M. Badr (MD)**

Lecturer of Pediatrics

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2013

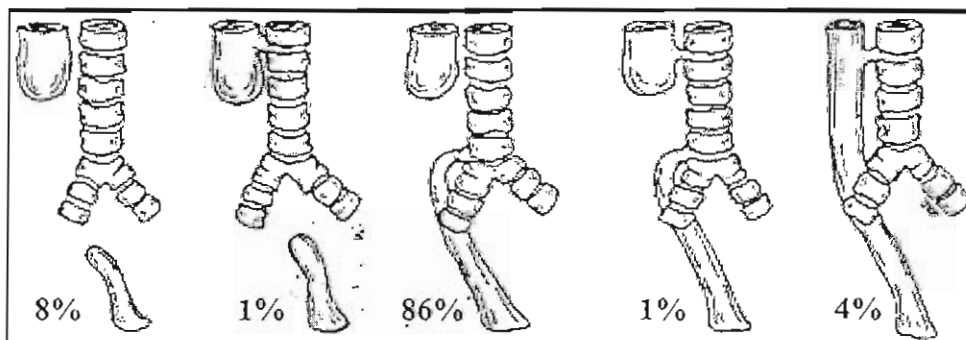
# **Congenital Anomalies of the GIT**

## **Esophageal Atresia & Tracheo-Esophageal Fistula**

### **Incidence**

- The most common congenital anomaly of the esophagus
- 1:4000 neonates

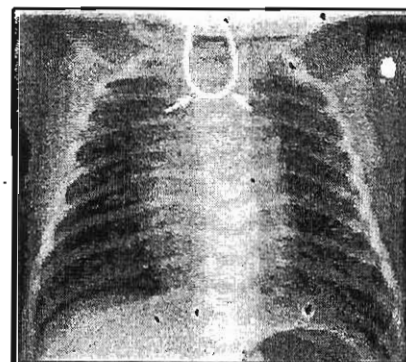
### **Types**



- The most common type is atresia with TEF is connected to the distal esophagus
- All types present in the neonatal period except H-shaped TEF (fistula without atresia)
- 50% are syndromic: VATER or VACTER, CHARGE (Coloboma, CVS, Heart, choanal Atresia, Retardation, Genital, Ear anomalies)

### **Clinical Picture**

- History of polyhydramnios
- Excessive salivation
- Neonatal respiratory distress
- Coughing, Choking & Cyanosis (With feeding)
- Failure to pass a catheter into the stomach
- H-shaped TEF may present **later** with recurrent aspiration, wheezes & chest infections



### **Investigations**

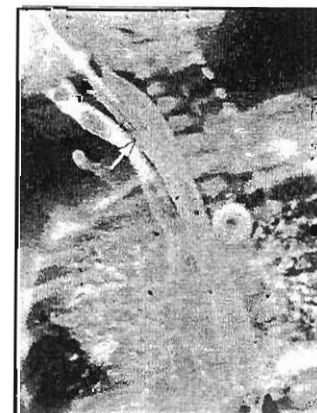
- X-ray: Coiling of the NGT (**airless** abdomen indicates...)
- H-shaped: Barium swallow (orifice can be detected at bronchoscopy)

### **Treatment**

- Stabilization & respiratory support (suctioning)
- Surgical correction (1ry repair or neo-esophagus using colonic segment)

### **Prognosis**

- Survival > 90%
- Complications: Leakage, stricture
- Associated GERD & tracheomalacia



# **Congenital Hypertrophic Pyloric Stenosis**

## **Incidence**

- 1-3:1000 (More in B & O blood groups)
- ♂:♀ ratio: 4:1

## **Etiology**

- Multifactorial (Genetic & environmental factors)
- Maternal macrolides & Erythromycin (If given in the 1<sup>st</sup> 2 wks): ↑↑ the incidence of CHPS

## **Pathology**

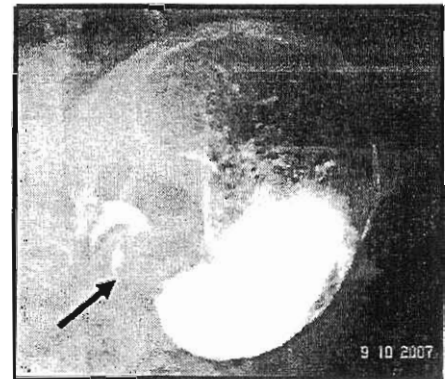
- Hypertrophy of the pyloric muscle resulting in gastric outlet obstruction (Not at birth)

## **Clinical Picture**

- Onset of symptoms: 3-6 wks **after** birth
- Repeated, progressive, nonbilious, projectile vomiting immediately after feeds
- The infant is hungry after vomiting
- Weight loss & Dehydration
- Olive-shaped, firm epigastric mass (*easiest after vomiting*)
- Visible peristalsis after feeding

## **Investigations**

- Hypochloremic metabolic alkalosis
- Prolonged neonatal jaundice (UCB)
- Abdominal US: Sensitivity 95%
- Barium meal: Narrow pyloric canal "String sign" ⇒



## **Differential Diagnosis**

- GERD, CAH, IEM
- Other causes of vomiting

## **Treatment**

- Stabilization
- Pyloromyotomy (Ramstedt)

# **Congenital Gastric Outlet Obstruction**

## **Incidence** Rare

## **Causes**

1. Pyloric atresia: More severe (Association with EB is known)
2. Antral web
3. Gastric duplication: Cystic or tubular structure within the wall of the stomach

## **Clinical Picture**

- History of polyhydramnios (majority)
- ↑↑ Gastric aspirate (at birth)
- Nonbilious vomiting, abdominal distention during the 1st day of life
- Gastric perforation may occur

## **Investigations**

- Plain X-ray, US, Barium meal, Endoscopy

## **Treatment**

- Stabilization
- Surgical or endoscopic repair

# Gastric Volvulus

## Definition

- Stomach twists on itself
- Abnormality of the gastric suspensory ligaments; Gastrohepatic, -splenic, -colic, -phrenic

## Types

- Organoaxial volvulus (Longitudinal axis)
- Mesenteroaxial volvulus (Transverse axis)

## Clinical Picture

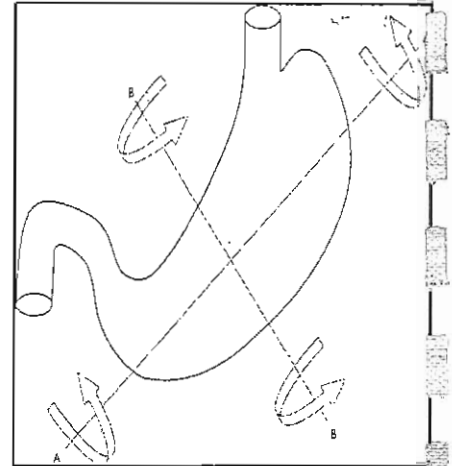
- Infancy: Nonbilious vomiting
- Older: Vomiting & abdominal pain
- Acute volvulus: may lead to strangulation and perforation.

## Investigations

- Plain X-ray, US, Barium meal

## Treatment

- Acute gastric volvulus: Stabilization & emergent surgery
- Laparoscopic gastropexy



# Intestinal Atresia & Stenosis

## Incidence

- 1:500 live birth (*Intestinal obstruction*)

## Pathogenesis

- Obstruction → Distension → Stasis & devitalization of the bowel
- Bowel dilatation → ↓↓ intestinal absorption & ↑↑ secretion of fluid and electrolytes
- Initial hypermotility followed by hypomotility
- Hypovolemia & hypokalemia
- Bacterial translocation & sepsis

## Classification (Of intestinal obstruction)

- ☑ Site: Duodenal, jejuna, ileal or colonic atresia/stenosis
- ☑ Cause: Intrinsic (Atresia, meconium plug) or extrinsic (Duplication, annular pancreas)
- ☑ Type: Simple or strangulation (impaired blood supply)
- ☑ Severity: Complete or partial

## Clinical Picture

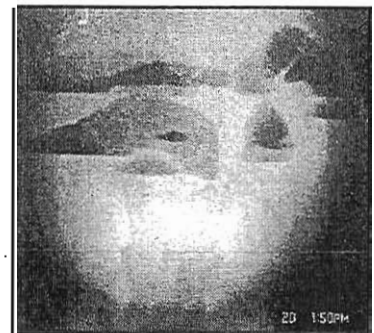
- Vomiting (bilious if the level of obstruction below the ampula of Vater)
- Constipation
- Abdominal distension: More in low intestinal obstruction
- ↑↑ Gastric aspirate (> 10-15 ml)

## Investigations

- Plain X-ray abdomen: Bowel distension & multiple air-fluid levels
- US: Distension
- Enema: Sometimes diagnostic and may be therapeutic

## Treatment

- NPO, IVF, NGT
- Surgical correction





# Malrotation

## Definition

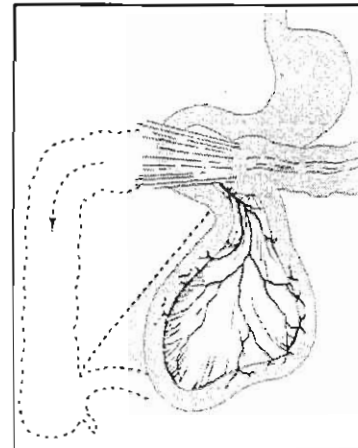
- Incomplete rotation of the intestine during fetal development
- The **small bowel** is found predominantly on the Rt side of the abdomen
- The small intestine has a narrow base ( $\uparrow\uparrow$  risk of **volvulus** & intestinal ischemia)

## Incidence

- 1:500- 1:6.000 live birth

## Clinical Picture

- May be asymptomatic
- Onset: 1<sup>st</sup> yr of life\*
- Acute volvulus: Bilious vomiting, abdominal pain
- Intermittent volvulus
- Recurrent episodes of vomiting, abdominal pain
- Acute IO (without previous bowel surgery) is suggestive



## Investigations

- Plain X-ray: Non-specific
- US
- Upper GI series (Follow-through): Modality of choice

## Treatment

- Acute gastric volvulus: emergent surgery
- Surgery: Correction of the malrotation (*counterclockwise rotation of the bowel*)

# Meckel Diverticulum

## Definition

- Meckel diverticulum is a remnant of the embryonic omphalomesenteric (Vitelline) duct
- Usually lined with ectopic acid-secreting mucosa

## Incidence

- 2-3% live birth (most common GIT anomaly)

## Clinical Picture

- May be asymptomatic
- Recurrent painless rectal bleeding (*Origin of blood?*)
- Intussusception (lead point)
- Diverticulitis: As appendicitis

### **Meckel diverticulum:**

- **Site:** 50-75 cm from IC valve
- **Length:** 3-6 cm
- **Side:** Antimesenteric border
- **Frequency:** 2-3%

## Investigations Difficult

- Plain X-ray, US: No value
- Barium study: rarely fill the diverticulum
- **Meckel radionuclide scan** (IV technetium-99m): *The most sensitive*
  - Sensitivity: 85%
  - Specificity: 95%
- Radio-labeled tagged RBC: Only if there is active bleeding

## Treatment

- Surgical excision

# Constipation

## Definition

- **Infrequent** passage of stools or the passage of **hard** stools
- This definition is **relative** (Depending on stool frequency, consistency & difficulty)
- A normal child may have a soft stool every 2-3 days
- A **hard** stool passed with **difficulty** every **3 days** should be treated as constipation
- Etiology may be due to defect in rectal filling (Hypothyroidism) or emptying (spinal cord)
- Most causes are **functional** (*No organic cause*)

## Etiology

### A) Functional (Idiopathic, nonorganic or fecal withholding):

- Typically started **after** the neonatal period
- It is due to voluntary withholding due to painful defecation (anal fissure, perianal inflammation...), aggressive potty training in a resistive child or lack of privacy
- PR examination: Large volume of stool with dilated rectum
- Encopresis is common, why? *Loss of rectal sensation*
- No organic cause: *Mention*

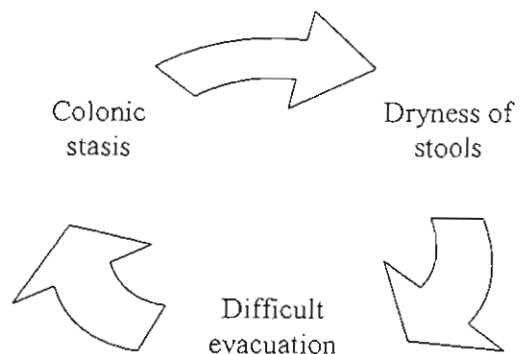
### B) Organic

1. Anatomical: Imperforate anus, intestinal stricture
2. Spinal cord defects: Neural tube defects (Dyraphism) →
3. Intestinal nerve or muscle abnormalities:
  - Hirschsprung disease
  - Pseudo-obstruction: Congenital or acquired
4. Psychomotor retardation
  - Cerebral palsy
  - Down syndrome
5. Neuromuscular diseases
  - Myopathy & Myotonia
  - Prune-Bely syndrome: Absent abdominal wall muscles
6. Intestinal disorders
  - Cystic fibrosis & Celiac disease
  - Cow's milk protein allergy
  - Typhoid
  - Tumors
7. Drugs
  - Vitamin D intoxication
  - Anticholinergics
  - Antidepressants, narcotics, methylphenidate
  - Lead
  - Pancreatic enzymes (*Fibrosing colonopathy*)
8. Metabolic
  - Hypothyroidism
  - Hypokalemia & Hypercalcemia
  - RTA, DM, dehydration
9. CT diseases
  - SLE
  - Scleroderma
10. Psychiatric disorders
  - Anorexia nervosa

### Neural tube defects:

- Spina bifida occulta
- Meningocele
- Meningomyelocele
- Encephalocele
- Anencephaly
- Dermal sinus
- Tethered cord
- Syringomyelia
- Diastomatomyelia
- Lipoma involving the conus

Defecation reflex is initiated by pressure receptors in the rectum



## Investigations

### Treatment

- ☒ Explanation & positive reinforcement
- ☒ Bowel training program: Sitting on the toilet for 5-10 min after meals
- ☒ ↑↑ Fluids & ↑↑ Fiber intake (vegetables & bran)
- ☒ Medications for disimpaction: Glycerin suppositories, PO<sub>4</sub> enemas, Polyethelene glycol
- ☒ Long-term treatment:
  - Softeners: Lactulose, sorbitol, paraffin oil (*Mineral oil*)
  - Stimulants: Senna (*Senekot*) "Prolonged use should be avoided"
  - Polyethylene glycol (*Non-absorbed laxative*)
- ☒ Treatment of the cause: Anal fissure...

## Hirschsprung Disease

(Congenital Aganglionic Megacolon)

### Pathology

- Absence of ganglionic cells in the myenteric & submucosal plexuses of rectum & variable distance of the colon (**Neurocristopathy; arrest of neuroblast migration**)
- Rectosigmoid (80%), long segment (15%), total bowel (5%)
- Failure of relaxation of the bowel wall (Obstruction)
- Distension → Stasis & devitalization → Enterocolitis (*Cl. Difficile, Staph., anaerobes*)

### Incidence

1:5.000 live birth (M:F = 4:1), sporadic (AD & AR have been demonstrated)

**Associations** Down syndrome, Ondine's curse, CVS or urogenital anomalies

### Clinical Picture

- A) Neonatal period: Delayed passage of meconium, IO, Hirschsprung's enterocolitis  
 B) Childhood: Chronic constipation

### Investigations

- Barium enema
- Anorectal manometry
- Suction rectal biopsy: Gold standard

#### PR examination in Hirschsprung

- Narrow segment
- Gush of liquid stools & flatus

**Treatment** Surgical (Usually 1 stage; 1ry pull-through procedure), may be laparoscopic

	Functional constipation	Hirschsprung Disease
Onset	> 2 yrs	At birth
Encopresis	Common	Very rare
FTT	Uncommon	May occur
Forced bowel training	Usual	No
Abdominal distension	Uncommon	Common (Fecal masses)
Anal tone	Normal	Normal
PR examination	Stool in ampulla	Ampulla empty
Barium enema	No transition zone	Transition zone (& delayed films)
Rectal biopsy	Normal	No ganglion cells
Anorectal manometry	Distension of the rectum causes relaxation of the internal sphincter	No sphincter relaxation
Treatment	See before	Surgical

# Encopresis & Fecal Soiling

## Definition & Epidemiology

- Passage of feces into inappropriate places after the expected age of control ( $\approx$  4 yrs)
- May be **primary** "*persists from infancy*" or **secondary** "*after successful toilet training*"
- It affects 1% of school-aged children
- Encopresis is more common in **boys** (4:1)
- Encopresis should not be diagnosed in cases of laxative abuse or general medical conditions

## Classification

A) **Retentive (80%)**: With constipation (Overflow incontinence), how? Causes?

- Fecal soiling may be presumed to be diarrhea
- Symptoms: Difficulty with defecation, abdominal pain

B) **Non-retentive**: Without constipation

## Risk Factors

- Constipation & anal fissure
- Stress: Death in the family, new child birth, neglect
- Psychological: Emotional problems, poor child-family relationship
- Sexual abuse

## Treatment

- ☒ Treatment of constipation
- ☒ Psychotherapy, behavioral management & star chart
- ☒ Biofeedback

# GIT Obstruction

	Congenital	Acquired
Esophagus	Esophageal atresia	Foreign body
	Tracheobronchial remnant	Stricture
	Vascular rings	Achalasia
	Schatzki ring ( <i>narrowing of the lower part of the esophagus</i> )	Chagas disease ( <i>Trypanosomiasis</i> )
		Collagen vascular disease
Stomach	Antral webs	Bezoar, foreign body
	Pyloric stenosis	Pyloric stricture (ulcer)
	Gastric duplication	Chronic granulomatous disease (CGD)
	Gastric volvulus	Eosinophilic gastroenteritis
		Crohn disease
Small Intestine	Duodenal atresia	Postsurgical adhesions
	Annular pancreas	Crohn disease
	Malrotation/volvulus	Intussusception
	Malrotation/Ladd bands	Distal ileal obstruction syndrome (CF)
	Ileal atresia	Duodenal hematoma
	Meconium ileus	Superior mesenteric artery syndrome
	Meckel diverticulum with volvulus or intussusceptions	
	Inguinal hernia	
	Intestinal duplication	
Colon	Meconium plug	Ulcerative colitis (toxic megacolon)
	Hirschsprung disease	Crohn disease
	Colonic atresia, stenosis	Chagas disease ( <i>Trypanosomiasis</i> )
	Imperforate anus	Fibrosing colonopathy (cystic fibrosis)
	Rectal stenosis	
	Pseudo-obstruction	
	Volvulus	
	Colonic duplication	

# Diarrhea

## Definition

- Increased Frequency &/or Fluidity of the stools deviated from the normal habit
- Infant stools = 5 gm/ Kg/ day
- Adult stools = 200 gm/ day

## Pathogenesis (= Mechanisms of diarrhea)

1. Osmotic
2. Secretory
3. Motility (↑↑ or ↓↓)
4. ↓↓ Surface area (Motility & Osmotic, how?)
5. Mucosal invasion (Shigella, Salmonella, amebiasis...)
6. Combined (HIV infection; malnutrition, ID, infection)

<b>Stool Ion Gap =</b> $\text{Stool osmolality} - 2 (\text{Na} + \text{K})$
--

	Osmotic diarrhea	Secretory diarrhea
<b>Frequency</b>	More common	Less common
<b>Defect</b>	Maldigestion Malabsorption Transport defect (Intestinal damage) Intake of unabsorbable substances	Active electrolyte & H <sub>2</sub> O secretion (↑↑ cAMP or ↑↑ cGMP)
<b>Volume</b>	< 200 cc	> 200 cc
<b>Osmolality</b>	↑↑ Osmolality	Normal Osmolality
<b>Ion gap</b>	> 100 mOsm/Kg	< 100 mOsm/Kg
<b>Stools ex.</b>	Watery Acidic (Stool pH < 5) Reducing substances Stool Na < 70 mEq / L	Watery Not acidic (Stool pH > 6) No Reducing substances Stool Na > 70 mEq / L
<b>Fasting</b>	Stops with fasting	Persists during fasting
<b>Examples</b>	<ul style="list-style-type: none"> <li>▪ Lactase deficiency (Disaccharidase)</li> <li>▪ Transport: Glu-Gal. malabsorption</li> <li>▪ Maldigestion: CF, Crohn...</li> <li>▪ Drugs (Lactulose, laxatives...)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cholera &amp; ETEC</li> <li>▪ Congenital Na &amp; Cl diarrhea</li> <li>▪ Carcinoid</li> <li>▪ VIP, neuroblastoma</li> </ul>

	↑↑Motility	↓↓Motility	↓↓Surface area
<b>Defect</b>	↓↓ Transit time	Stasis (↑↑ Bacteria)	↓↓ Functional capacity
<b>Stool</b>	Loose to normal	Loose to normal	Watery
<b>Examples</b>	<ul style="list-style-type: none"> <li>▪ Thyrotoxicosis</li> <li>▪ Irritable bowel syndrome</li> <li>▪ Dumping syndrome "Post-vagotomy"</li> </ul>	<ul style="list-style-type: none"> <li>▪ Blind loop</li> <li>▪ Intestinal pseudoobstruction</li> </ul>	<ul style="list-style-type: none"> <li>▪ Short bowel syndrome</li> <li>▪ Celiac disease</li> </ul>

## Classification

Duration	Etiology
<b>A) Acute:</b> < 2 wks <b>B) Persistent:</b> Begins acute & lasts ≥ 14 days <b>C) Chronic:</b> ≥ 14 days	<b>A) Infective:</b> Gastroenteritis <b>B) Non-infective:</b> Diet, antibiotics...

# Acute Gastroenteritis

**Definition** Acute infective diarrhea

## Epidemiology

- ☑ Major pediatric problem [50% of infant mortality]
- ☑ More serious in infants [↑↑ Risk of fluid & electrolyte disturbances], Why?
  - Infants have greater surface area to weight ratio leading to ↑↑ insensible water loss
  - Inability to gain access to fluids when thirsty
  - Immature renal tubular reabsorption function
- ☑ Risk factors for GE:
  - Environmental contamination
  - Lack of breastfeeding
  - Nutritional deficiencies: Malnutrition, Vitamin A & Zn deficiency
  - Immunodeficiency

**Etiology** (Of acute diarrhea)

### A) Infective diarrhea (= Gastroenteritis)

- ☑ Bacterial (*More serious, more in Summer*)
  - Salmonella
  - Shigella
  - Staphylococci
  - Yesinia enterocolitica
  - E. coli
  - Campylobacter jejuni
  - Cholera
- ☑ Viral (*Commoner in winter*)
  - Rotavirus & Adenovirus
- ☑ Parasitic (*Usually not severe*)
  - Entameba histolytica
  - Giardia lamblia



### B) Non-infective diarrhea

- ☑ Diet: Over feeding, irregular feeding or inappropriate foods, poisoning
- ☑ Drug: Antibiotics specially oral ampicillin
- ☑ Diseases: Parenteral diarrhea (Respiratory or UTI)

## Pathophysiology

	Enterotoxigenic	Enteroinvasive
<b>Mechanism</b>	<ul style="list-style-type: none"> <li>▪ Organism <u>adheres</u> to the mucosal cells</li> <li>▪ No penetration</li> <li>▪ Secrete toxins</li> <li>▪ ↓↓ Cl &amp; H<sub>2</sub>O absorption</li> <li>▪ ↑↑ Intestinal secretion</li> </ul>	<ul style="list-style-type: none"> <li>▪ Organism <u>invades</u> the cells</li> <li>▪ Penetration</li> <li>▪ Inflammation</li> <li>▪ ↓↓ Cl &amp; H<sub>2</sub>O absorption</li> <li>▪ Exudation of blood</li> </ul>
<b>Pathology</b>	Intact cells	Inflammation, exudation
<b>Metabolic</b> ≠	Fluid & electrolyte disturbances	Toxic manifestations
<b>C/P</b>	Watery diarrhea	Bloody diarrhea
<b>Examples</b>	<ul style="list-style-type: none"> <li>▪ Enterotoxigenic E. coli</li> <li>▪ Cholera</li> <li>▪ Staphylococci</li> </ul>	<ul style="list-style-type: none"> <li>▪ Enteroinvasive E. coli</li> <li>▪ Salmonella</li> <li>▪ Shigella</li> <li>▪ Yesinia enterocolitica</li> <li>▪ Campylobacter jejuni</li> </ul>

## Clinical Evaluation

A) Severity of the diarrhea

B) Associated symptoms

- Fever (High fever suggests bacterial infection), vomiting, abdominal pain

C) Causative organisms

	Watery diarrhea	Bloody diarrhea
Bacteria	<ul style="list-style-type: none"> <li>Enterotoxigenic E. coli</li> <li>Cholera</li> <li>Staphylococci</li> </ul>	<ul style="list-style-type: none"> <li>Enteroinvasive E. coli</li> <li>Salmonella</li> <li>Shigella</li> <li>Yersinia enterocolitica</li> <li>Campylobacter jejuni</li> </ul>
Viral	Rotavirus	-
Parasites	Giardia lamblia	Entamoeba histolytica

## D) Complications

### 1. Dehydration

☒ Cause: Loss of ECF

☒ Manifestations: Sunken eyes, depressed AF, dry tongue, lost skin turgor, oliguria

### 2. Shock

☒ Cause: Hypovolemic shock (Loss of ECF), Septic shock may also occur

☒ Manifestations: Tachycardia, hypotension, poor peripheral perfusion

### 3. Acute renal failure

☒ Cause: ↓↓ Renal perfusion (Prerenal failure)

☒ Manifestations: Oliguria or anuria

### 4. Metabolic acidosis

☒ Cause: Lactic acidosis (Tissue hypoperfusion) & Renal failure

☒ Manifestations: Deep rapid respiration (Acidotic breathing)

### 5. Hypokalemia

☒ Cause: ↓↓ Intake & ↑↑ Intestinal loss

☒ Manifestations: Abdominal distension & paralytic ileus

### 6. Hypocalcemia

☒ Cause: ↓↓ Intake & ↑↑ Intestinal loss

☒ Manifestations: Tetany (Carpo-pedal spasm) & Convulsions

### 7. Bleeding

☒ Cause: Hypoprothrombinemia (↓↓ Vitamin K) & DIC

☒ Manifestations: Bleeding (?ICH)

### 8. Convulsions

☒ Cause: Febrile, ICH, Metabolic (↓↓ Ca, ↓↓ Na, ↑↑ Na), Toxic (Salmonella, Shigella)

☒ Manifestations: Variable types of convulsions (Focal, generalized...)

### 9. Persistent diarrhea

☒ Cause: Lactose intolerance, persistent infection, cow' milk protein allergy, bacterial overgrowth

☒ Manifestations: Diarrhea ≥ 14 days

### 10. Malnutrition

☒ Cause: ↓↓ Calories (Marasmus), wrong feeding with excess CHO (Kwashiorkor)

☒ Manifestations: Wasting (Marasmus), Edema (Kwashiorkor)

### Remember

#### Acute Renal Failure

- Pre-renal
- Intrinsic renal
- Post-renal



## Biochemical changes in GE

1. Diarrhea  $\rightarrow$   $\downarrow\downarrow$   $H_2O$ ,  $\downarrow\downarrow$   $HCO_3$ ,  $\downarrow\downarrow$   $K$   $\rightarrow$  Dehydration & Acidosis
2. Vomiting  $\rightarrow$   $\downarrow\downarrow$   $H_2O$ ,  $\downarrow\downarrow$   $HCl$   $\rightarrow$  Dehydration & Alkalosis
3. GE = Diarrhea & Vomiting
4. Usually diarrhea is more severe than vomiting
5. Net result: Dehydration & Acidosis

## Extra-Intestinal manifestations of Enteric Infections

Manifestation	Organisms	Notes
<b>Focal infections</b> (Systemic spread) UTI, IE, pneumonia, hepatitis, peritonitis	All major pathogens, Salmonella, Shigella, Yersinia, Campylobacter, C. difficile	<ul style="list-style-type: none"> <li>▪ Onset: Early or delayed</li> <li>▪ Prognosis: Depends on the site</li> </ul>
<b>Reactive arthritis</b>	Salmonella, Shigella, Yersinia, Campylobacter, C. difficile, Cryptosporidium	<ul style="list-style-type: none"> <li>▪ Onset: 1-3 wk after infection</li> <li>▪ Most recover within 2-6 mo</li> </ul>
<b>Guillain-Barre syndrome</b>	Campylobacter	<ul style="list-style-type: none"> <li>▪ Onset: Few weeks after infection</li> </ul>
<b>Glomerulonephritis</b>	Campylobacter, Yersinia, Shigella	<ul style="list-style-type: none"> <li>▪ Acute or chronic GN</li> <li>▪ Recovery is usual</li> </ul>
<b>IgA nephropathy</b>	Campylobacter	IgA nephropathy
<b>Erythema nodosum</b>	Campylobacter, Yersinia, Salmonella	<ul style="list-style-type: none"> <li>▪ Tender erythematous nodules on the shins, thigh or forearm</li> <li>▪ Resolves with 4-6 wk</li> </ul>
<b>HUS</b>	Shigella dysenteriae, E. coli O157:H7	ARF
<b>Hemolytic anemia</b>	Campylobacter, Yersinia	Rare

## Investigations

### A) To identify the causative organism

- Stool analysis: Parasites (E. histolytica & G. lamblia), WBCs (Bacterial etiology)
- Stool culture & Sensitivity: Bacteria
- CBC, CRP, ESR, Blood culture: help in diagnosis of bacterial infections

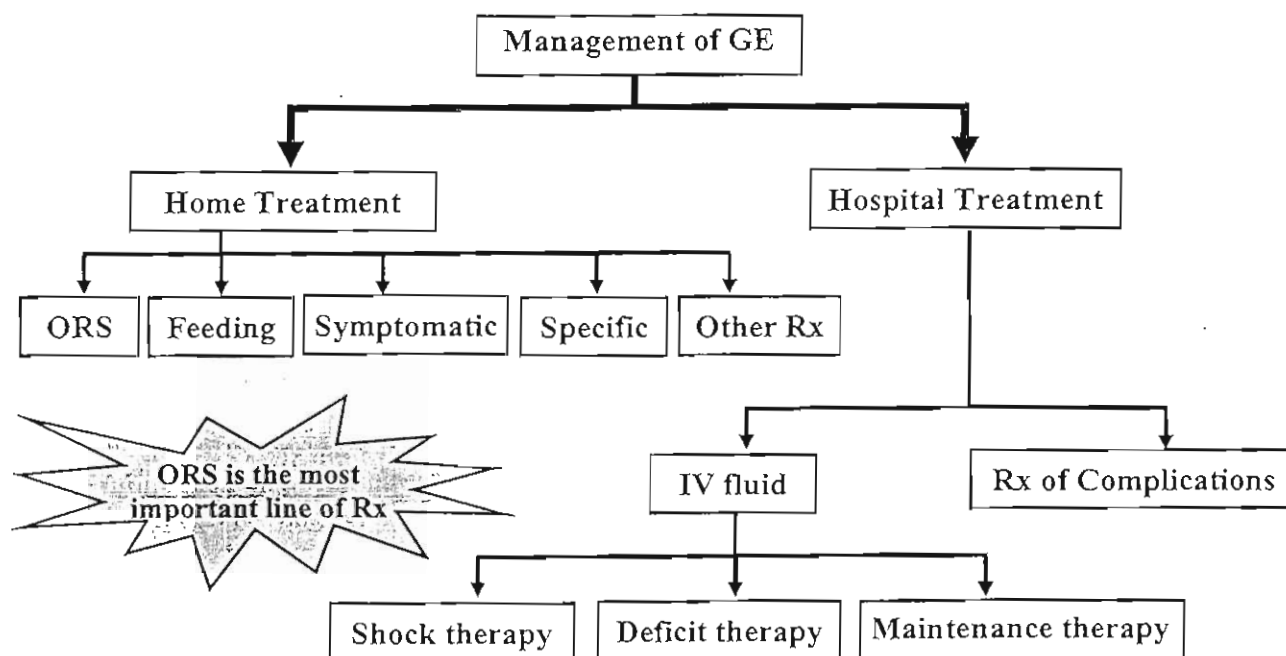
### B) To detect complications

- KFTs (Urea & Creatinine): Renal failure
- Electrolytes: Na, Ca, K
- Blood gases: Metabolic acidosis
- $\uparrow\uparrow$  PT,  $\uparrow\uparrow$  PTT,  $\downarrow\downarrow$  Platelet count, +Ve FDPs: DIC

### Important Notes

- Dehydration (Not diarrhea alone) is the main cause of morbidity & mortality
- Correction of dehydration is the mainstay of treatment
- Throughout the world, ORS saves the lives of millions of children each year
- Enteral nutrition is essential for gut integrity
- Intestinal mucosa undergoes continuous shedding (every 5-7 days)
- GE is a self-limited (No need for routine antibiotic therapy)

# Treatment of Gastroenteritis



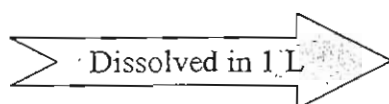
## A) Home management

### 1. Oral rehydration therapy

☒ Importance: ORS is the most important line of Rx

☒ Composition

▪ NaCl:	3.5 gm
▪ Na Citrate:	2.5 gm
▪ K Cl:	1.5 gm
▪ Glucose:	20 gm



▪ Na:	90 mEq
▪ Cl:	80 mEq
▪ K:	20 mEq
▪ Glucose:	111 mmol

☒ Another type of ORS is available with lower Na content (↓↓ risk of Hypermnatremia)

☒ Principle: Glucose-facilitated Na absorption (ORS will not stop diarrhea)

☒ Amount:

- Diarrhea with **No dehydration**: 50-100 ml after each loose stools
- 50-100 ml/Kg according to the degree of **dehydration** over 4-6 hrs
- Mild to moderate dehydration: 50-100 ml/Kg
- Thirst mechanism is effective in regulating the received amount

☒ Indications:

- Prevention of dehydration
- Mild & moderate dehydration
- **All** types of dehydration with Na concentration between 115-165 mEq/L
- **All** age groups including neonates
- **All** types of micro-organisms (Viral, Bacterial, Parasitic)

☒ Methods:

- Oral: Cup & spoon (*One 5 ml spoon every 1-2 minutes*)
- If the child vomits, wait for 10 minutes. Then continue but more slowly
- Nasogastric tube is indicated in the following conditions:
  - Unconscious child
  - Uncooperative mother
  - Refusal of ORS
  - Persistent vomiting (with oral Rx; Ondansetron is effective)

### ☒ Composition of available ORS & Coca-Cola

ORS	CHO	Na	K	Cl	Base	Osmolality
Low osmolality ORS	13.5	75	20	65	10	245
WHO (1975)	20	90	20	80	10	311
Coca-Cola	112	1.6	-	-	13.4	650

## 2. Feeding

☒ **Rational:** Enteral nutrition is essential for gut integrity

Delayed feeding → ↓↓ Repair of intestinal mucosa & persistent diarrhea

☒ **Timing:** Once rehydration is complete (Replacement of losses should be continued)

☒ **Method:**

a. **Breast-fed infants:** Breast milk is given (as the child wants) with ORS therapy

b. **Formula-fed infants:** Non-diluted formula should be resumed as soon as possible according to the child tolerance

c. **Older children:** Gradual introduction of solid foods as vegetables, fruits, potatoes, yogurt & jellies with gradual ↑↑ the amount according to the tolerance

☒ **Avoid:** Fatty foods, tea, foods with rich in simple sugars (carbonated soda & juices)

☒ Most children can tolerate milk & lactose-containing diet

## 3. Symptomatic therapy

☒ **Vomiting:** Antiemetics (Ondansetron, Domperidone, Metoclopramide...)

☒ **Fever:** Antipyretics (Paracetamol, ibuprofen...)

☒ **Diarrhea:** Anti-diarrheal drugs have **No** scientific role

Anti-motility drugs are absolutely **contraindicated**

## 4. Specific therapy

☒ **Rational:**

- GE is self-limited disease, why? (Shedding of epithelial cells with organisms)
- Not all causes are due to bacterial infection (Viral & Parasitic)
- Antibiotics may interfere with normal intestinal flora (↑↑ Pathogens)

☒ **Drugs:**

a. **Parasites:**

- Entameba histolytica: Metronidazole (50 mg/Kg/day) for 10 days
- Giardia lamblia: Metronidazole (25 mg/Kg/day) for 7 days

b. **Antibiotics:** are indicated only in the following conditions:

- Cholera: Tetracyclin
- Shigella: Ampicillin or 3<sup>rd</sup> generation cephalosporin
- Salmonella: Ampicillin or 3<sup>rd</sup> generation cephalosporin

## 5. Zinc supplementation

- ↓↓ Severity, duration & recurrence of GE
- Dose: 10-20 mg/day for 10-14 days

## 6. Other therapies

☒ **Probiotics:**

- **Value:** Restore beneficial flora & ↓↓ pro-inflammatory cytokines
- **Examples:** Lactobacillus bifidobacterium, Saccharomyces boulardii

☒ **Nitazoxanide:**

- Anti-infective agent
- **Effective in the TTT of:** G. lamblia, E. histolytica, C. difficile, rotavirus

☒ **Enkephalinase inhibitor (Racecadotril):** ↓↓ intestinal ion secretion

## B) Hospital management

### Indications

- Severe dehydration
- Severe persistent vomiting
- Failure or deterioration on home management
- Complications: ARF, bleeding, convulsions...

### 1. IV Rehydration therapy

#### a. Shock (Over 1 hr):

- Type: Lactated ringer's
- Dose: 20 ml/Kg over 1 hr

#### b. Deficits (Over 8 hrs):

- Type: Normal saline:Glucose 5% [Ratio = 1:1] + KCl (1ml for each 100 ml)
- Dose:
  - Mild dehydration: 40 ml/Kg
  - Moderate dehydration: 80 ml/Kg
  - Severe dehydration: 120 ml/Kg

#### c. Maintenance (Over 24 hrs):

- Type: Glucose 5% :Normal saline[Ratio = 4:1] + KCl (1ml for each 100 ml)
- Dose:
  - 1<sup>st</sup> 10 Kg: 100 ml/Kg
  - 2<sup>nd</sup> 10 Kg: 50 ml/Kg
  - 3<sup>rd</sup> 10 Kg: 20 ml/Kg

#### d. Important notes

- KCl should be added to the fluid used in maintenance & deficit therapy; 1 ml for each 100 ml of IVF
- In **hypernatremic** dehydration: Only 70% of the calculated volume & should be given slowly to prevent the development of brain edema

### 2. Treatment of Complications

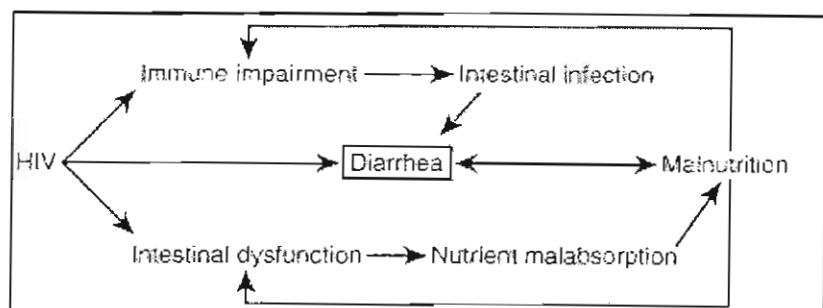
- a. Metabolic acidosis:  $\text{NaHCO}_3$
- b. ARF: Fluid balance, dialysis
- c. Septic shock: Antibiotics
- d. Convulsions: Anticonvulsants (Diazepam)
- e. Bleeding: Vitamin K, FFP, blood transfusion

#### Hypernatremic dehydration:

- ↓↓ Volume
- ↓↓ Rate

### Prevention

- Promotion of breastfeeding
- Nutritional education
- Promotion of personal hygiene
- Rotavirus immunization
- Improved water supply & sanitary facilities
- Proper management of GE



# Dehydration

## Definition

**Dehydration:** Loss of ECF, the ICF may suffer secondarily

**Types:** Isotonic, Hypertonic & Hypotonic

**Grades:** Mild, Moderate & Severe

## Types

	Isotonic	Hypertonic	Hypotonic
<b>Incidence</b>	75 %	15 %	10 %
<b>Serum Na</b>	130-150 mEq/L	> 150 mEq/L	< 130 mEq/L
<b>Etiology</b>	<ul style="list-style-type: none"> <li>Acute GE</li> <li>Fasting (Deprivation of foods &amp; water)</li> </ul>	<ul style="list-style-type: none"> <li>↓ ↓ H<sub>2</sub>O intake (CP), ↑ ↑ Na (ORS)</li> <li>Severe vomiting, DKA, DI</li> </ul>	<ul style="list-style-type: none"> <li>Prolonged diarrhea in PEM</li> <li>Dehydration treated by hypotonic IVF</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>H<sub>2</sub>O &amp; Na are lost in the same proportion</li> <li>Isotonic ECF</li> <li>No shift between ECF &amp; ICF</li> <li>Normal cell hydration</li> <li>Decreased ECF</li> </ul>	<ul style="list-style-type: none"> <li>H<sub>2</sub>O loss &gt; Na loss</li> <li>Hypertonic ECF</li> <li>Shift of H<sub>2</sub>O from cells to ECF</li> <li>Cellular dehydration</li> <li>ECF is not markedly affected</li> </ul>	<ul style="list-style-type: none"> <li>Na loss &gt; H<sub>2</sub>O loss</li> <li>Hypotonic ECF</li> <li>Shift of H<sub>2</sub>O from ECF to cells</li> <li>Cellular edema</li> <li>ECF is markedly affected</li> </ul>
<b>Clinical Picture</b>			
<b>ECF</b>			
A. fontanel	Depressed	Mildly depressed	Markedly depressed
Eyes	Sunken	Mildly sunken	Markedly sunken
Skin turgor	Poor	Mildly affected	Very poor
Tongue	Dry	Very dry	Moist
<b>ICF</b>			
CNS	According to the degree (Lethargy-coma)	Irritability up to convulsions	Lethargy up to coma

## Clinical Grades of Dehydration

	Mild	Moderate	Severe
<b>Weight loss</b>	4 %	8 %	12 %
<b>A. fontanel</b>	Normal	Mildly depressed	Markedly depressed
<b>Eyes</b>	Mild	Moderate	Marked
<b>Skin turgor</b>	Mild	Moderate	Marked
<b>Tongue</b>	Dry (Normal)	Dry	Very dry
<b>CNS</b>	Conscious	Lethargy	Coma

# Persistent Diarrhea

## Definition

Diarrhea that **started** acutely but **persists** for  $\geq 14$  days

## Incidence

5-20% of acute GE

## Etiology

Disaccharidases are present on the brush border of the intestinal mucosal cells

### 1. Lactose intolerance

#### ☒ Pathogenesis

- Disaccharidases are present on the brush border of the intestinal villi
- GE destroys the brush border → Loss of disaccharidases (Mainly lactase)
- Sugar malabsorption: ↑↑ Lactose
  - Osmotic diarrhea
  - Acids (Acidic stools)
  - Gases (Abdominal distension)

Fermentation

#### ☒ Diagnosis

- Watery diarrhea
- Stool analysis: Acidic stools + Reducing substances

### 2. Cow's milk protein allergy

#### ☒ Pathogenesis

- Normally, the GIT is impermeable to cow's milk proteins
- Damage of the GIT wall (GE) → Intestinal allergy & inflammation
- Mucus & blood (Frank or occult) in stools

#### ☒ Diagnosis

- Withdrawal of cow's milk improves diarrhea (Reappear with reintroduction)
- Stool analysis: Mucus & blood in stools

### 3. Bacterial overgrowth in the upper small intestines

#### ☒ Pathogenesis

- Normally, the upper part of the small intestine is sterile
- After acute GE, colonic bacteria may invade the upper small intestines
- Bacterial invasion leads to damage of the mucosa → Persistent diarrhea

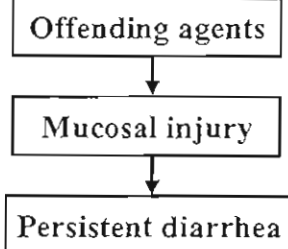
#### ☒ Diagnosis

- Stool analysis & Culture: Bacteria

### 4. Persistent infection: Giardiasis

## Pathogenesis

- Offending agents: Disaccharides, milk proteins, bacteria...
- Vicious circle



## Treatment

- Treatment is mainly dietetic (for long duration to help intestinal repair)
- Lactose intolerance: Lactose-free diet
- Cow's milk protein allergy: Soy bean-based formula (*Nursoy*)
- Hypoallergenic protein hydrolysate formula (*Pregestimil*): "See nutrition"
- Vitamins: Vitamin A
- Trace elements
- Total parenteral nutrition (TPN) may be needed

# Chronic Diarrhea

## Definition

Diarrhea lasting > 2 wks should be considered chronic

## Etiology

<b>1. Infections</b> <ul style="list-style-type: none"> <li>▪ Bacterial, viral and protozoan agents</li> <li>▪ Bacterial overgrowth</li> <li>▪ Postenteritis syndrome</li> <li>▪ Tropical sprue</li> <li>▪ Whipple disease</li> </ul>	<b>2. Exogenous substances</b> <ul style="list-style-type: none"> <li>▪ Carbonated fluid &amp; drinks containing methylxanthines (cola, tea, coffee)</li> <li>▪ Foods containing sorbitol, mannitol</li> <li>▪ Antacids or laxatives containing lactulose or <math>Mg(OH)_2</math></li> <li>▪ Bile acids sequestrants</li> </ul>
<b>3. Abnormal digestion</b> <ul style="list-style-type: none"> <li>▪ Cystic fibrosis</li> <li>▪ Shwachman-Diamond syndrome</li> <li>▪ Isolated pancreatic enzyme deficiency</li> <li>▪ Chronic pancreatitis</li> <li>▪ Pearson syndrome</li> <li>▪ Protein-calorie malnutrition</li> <li>▪ Trypsinogen and enterokinase deficiency</li> <li>▪ Chronic cholestasis</li> <li>▪ Terminal ileal resection</li> <li>▪ Primary bile acid malabsorption</li> </ul>	<b>4. Malabsorption</b> <ul style="list-style-type: none"> <li>▪ Lactase deficiency</li> <li>▪ Sucrase-isomaltase deficiency</li> <li>▪ Glucose-galactose malabsorption</li> <li>▪ Fructose malabsorption</li> <li>▪ Short bowel syndrome (Cong. or acquired)</li> </ul>
<b>5. Immune &amp; inflammatory</b> <ul style="list-style-type: none"> <li>▪ Food allergy (cow's milk, soy proteins...)</li> <li>▪ Celiac disease</li> <li>▪ Eosinophilic gastroenteritis</li> <li>▪ Inflammatory bowel disease</li> <li>▪ Autoimmune enteropathy</li> <li>▪ IPEX syndrome</li> <li>▪ Immunodeficiencies (1ry &amp; 2ry)</li> </ul>	<b>6. Transport defects</b> <ul style="list-style-type: none"> <li>▪ Congenital Na diarrhea</li> <li>▪ Congenital Cl diarrhea</li> <li>▪ Acrodermatitis enteropathica</li> <li>▪ Selective folate deficiency</li> <li>▪ Menkes syndrome (Kinky hair)</li> <li>▪ Abetalipoproteinemia</li> </ul>
<b>7. Neoplastic</b> <ul style="list-style-type: none"> <li>▪ Neuro-endocrine hormone-secreting tumors (APUDoma, VIPoma)</li> <li>▪ Pheochromocytoma</li> <li>▪ Zollinger-Ellison</li> <li>▪ Lymphoma</li> </ul>	<b>8. Structural defects</b> <ul style="list-style-type: none"> <li>▪ Microvillus inclusion disease</li> <li>▪ Tufting enteropathy</li> <li>▪ Phenotypic diarrhea (Dysmorphism &amp; Diarrhea)</li> <li>▪ Heparan-sulphate deficiency</li> <li>▪ Lymphangiectasia</li> </ul>
<b>9. Motility disorders</b> <ul style="list-style-type: none"> <li>▪ Hirschsprung disease</li> <li>▪ Chronic intestinal pseudo-obstruction</li> <li>▪ Thyrotoxicosis</li> </ul>	<b>10. Chronic nonspecific diarrhea</b> <ul style="list-style-type: none"> <li>▪ Irritable bowel syndrome [&gt; 5 yrs]</li> <li>▪ Toddler's (Functional) diarrhea [&lt; 4 yrs]</li> <li>▪ Toddler's diarrhea</li> </ul>

**IPEX:** Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

## Approach to a Case of Chronic Diarrhea

### (A) History:

- Age:
  - Neonate: Microvillus inclusion disease, Hirschprung's, lymphangiectasia
  - Infant: Tufting enteropathy, toddler's diarrhea, celiac, CF, post-GE diarrhea
  - Child: Irritable bowel, C.difficile, post-GE diarrhea, IBD
- Dietetic history
- History of preceding GE
- History of polyhydramnios: Congenital Na or Cl diarrhea
- History of asthma or eczema: Allergic
- History of arthritis, DM: Autoimmune

### (B) Physical examination:

- Facial dysmorphism: Phenotypic diarrhea
- Rash: Acrodermatitis enteropathica
- Weight, height/length, weight for height index: *Weight is affected before height*
- Nutritional status
- Assessment of body composition
  - Mid-arm circumference
  - Skin fold thickness
  - DEXA scan: Dual emission absorptiometry

### (C) Investigations:

1. Step 1
<ul style="list-style-type: none"> <li>▪ Stool analysis               <ul style="list-style-type: none"> <li>➤ Microbiology: Stool cultures, Microscopy for parasites, Viruses</li> <li>➤ Stool electrolytes</li> </ul> </li> <li>▪ H<sub>2</sub> breath test</li> <li>▪ Tests for celiac disease</li> <li>▪ Tests for food allergy: Prick &amp; patch and oral challenge</li> <li>▪ Non-invasive tests for malabsorption               <ul style="list-style-type: none"> <li>➤ Stool <math>\alpha</math>-1-AT, Reducing substances, Elastase</li> <li>➤ Stool leukocytes &amp; occult blood</li> <li>➤ Rectal NO</li> </ul> </li> </ul>
2. Step 2
<ul style="list-style-type: none"> <li>▪ Upper endoscopy &amp; jejuna biopsy: Multiple sites, why?</li> <li>▪ Lower endoscopy &amp; colonic biopsy, when?</li> <li>▪ Morphometry Quantitative epithelial changes</li> <li>▪ PAS staining</li> <li>▪ EM</li> <li>▪ Imaging: Plain X-ray, US, barium meal &amp; follow-through</li> </ul>
3. Step 3
<ul style="list-style-type: none"> <li>▪ Intestinal immunohistochemistry</li> <li>▪ Anti-enterocyte Ab &amp; Auto antibodies</li> <li>▪ <sup>75</sup>SeHCAT measurement: Homocholic acid-aurine is bile acid analog (BA malabsorption)</li> <li>▪ Brush border enzyme activity</li> <li>▪ Motility studies &amp; EPS</li> <li>▪ Serum catecholamines</li> <li>▪ Isotopic scanning for APUDoma</li> <li>▪ CT &amp; MRI</li> </ul>



## Treatment

### A. Nutritional rehabilitation

- Increase caloric intake
- Lactose intolerance: Lactose-free diet
- Sucrase-isomaltase deficiency: Sucrose-free diet
- Cow's milk protein allergy: Soy bean-based formula (*Nursoy*)
- Medium-chain TAG
- Semi-elemental or elemental diet
- Hypoallergenic protein hydrolysate formula (*Pregestimil*) or amino acid-based feeding

### B. Drug therapy

- Anti-infectious agents: SMX-TMP, nitazoxanide & metronidazole have a broad pattern
- Oral human immunoglobulins (300 mg/Kg)
- Immunosuppressives: Autoimmune enteropathy
- Octreotide (Somatostatin analog): Neuroendocrinal tumors, microvillus inclusion disease
- Zinc supplementation
- Growth hormone
- Enkephalinase inhibitor (Racecadotril): ↓↓ intestinal ion secretion

### C. Total parenteral nutrition (TPN)

### D. Intestinal transplantation

## Toddler Diarrhea

### Etiology

- ↑↑ Intake of carbonated fluids & fruit juice
- Low fat diet

### Clinical Picture

- Age: 1-3 yrs (♂ > ♀)
- Good health & thriving
- Stool: Watery, loose ↑↑ Intake of carbonated fluids & fruit juice

### Investigations

- Normal blood investigations
- Normal stool examination

### Treatment

- Reassurance
- ↑↑ Dietary fat
- ↓↓ Carbonated fluids & fruit juices

### Prognosis

- Spontaneous resolution by the age of 3-4 yrs

## Parental Diarrhea

### Definition

Diarrhea occurring with infection (Respiratory, UTI...)

### Etiology

- Unknown (Not cause-effect relationship)
- ?The same etiological agent
- ?Antibiotic-induced

# **Diarrhea from Neuroendocrine Tumors**

## **Definition**

Rare tumors of the neuroendocrine cells of the GIT, adrenal & extra-adrenal sites derived from the APUD system

## **Importance**

- Should be considered in cases of severe or chronic diarrhea, flushing or palpitations

## **Types**

NET	Site	Marker	C/P
<b>Carcinoid</b>	Intestinal argentaffin cells	Serotonin (5-HT)	Secretory diarrhea, abdominal cramps, flushing, wheezing, & cardiac valve damage
<b>Gastrinoma, Zollinger-Ellison syndrome</b>	Pancreas	Gastrin	peptic ulcers, secretory diarrhea
<b>Mastocytoma</b>	Skin, liver, spleen, small intestine	Histamine, VIP	Pruritus, flushing, apnea, diarrhea
<b>Medullary carcinoma</b>	Thyroid C-cells	Calcitonin, VIP, PGs	Secretory diarrhea
<b>Pheochromocytoma, Ganglioneuroma, Neuroblastoma, Ganglioneuroblastoma</b>	Chromaffin cells	Catecholamines, VIP (VMA in neuroblastoma)	HTN, tachycardia, palpitations, sweating, anxiety, watery diarrhea
<b>Somatostatinoma</b>	Pancreas	Somatostatin	Secretory diarrhea, steatorrhea, DM, cholelithiasis
<b>VIPoma</b>	Pancreas	VIP, PGs	Secretory diarrhea, achlorhydria, hypokalemia

## **Investigations**

- Whole-body MRI may be needed
- Peptide receptor scintigraphy

## **Treatment**

- Tumor resection is the treatment of choice but is potentially hazardous (adrenergic crises)
- Long-acting somatostatin analogs might also have a role

# Introduction of Malabsorption

## A) Carbohydrates

### Digestion:

- Starch: Salivary & pancreatic amylase
- Disaccharides: Brush border disaccharidases (Maltase, Sucrase, Lactase)
  - Maltose  $\Rightarrow$  Glucose + Glucose
  - Sucrose  $\Rightarrow$  Glucose + Fructose
  - Lactose  $\Rightarrow$  Glucose + Galactose

### Absorption:

- Glucose & galactose: Active symport (with Na)
- Fructose: Passive absorption

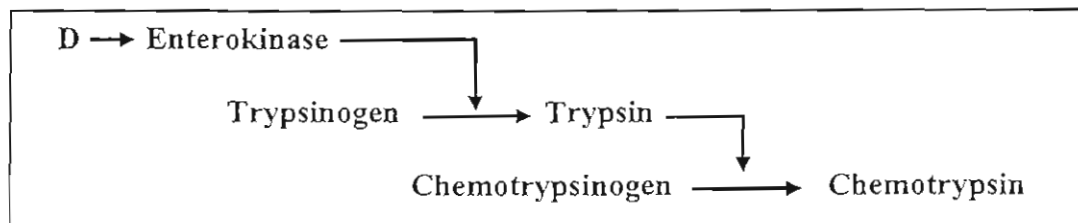
## B) Proteins

### Digestion:

- Stomach (Chief or peptic cell): Pepsin (Hydrolysis of proteins)
- Pancreas: Trypsin & Chemotrypsin [Activated by enterokinase]

### Absorption:

Aminoacids: Portal vein



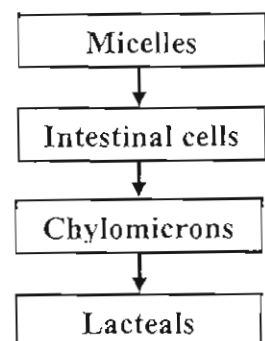
## C) Fats

### Digestion:

Lipases: Lingual, gastric, pancreatic & intestinal  
 Emulsification is essential (Bile salts & peristaltic movements)

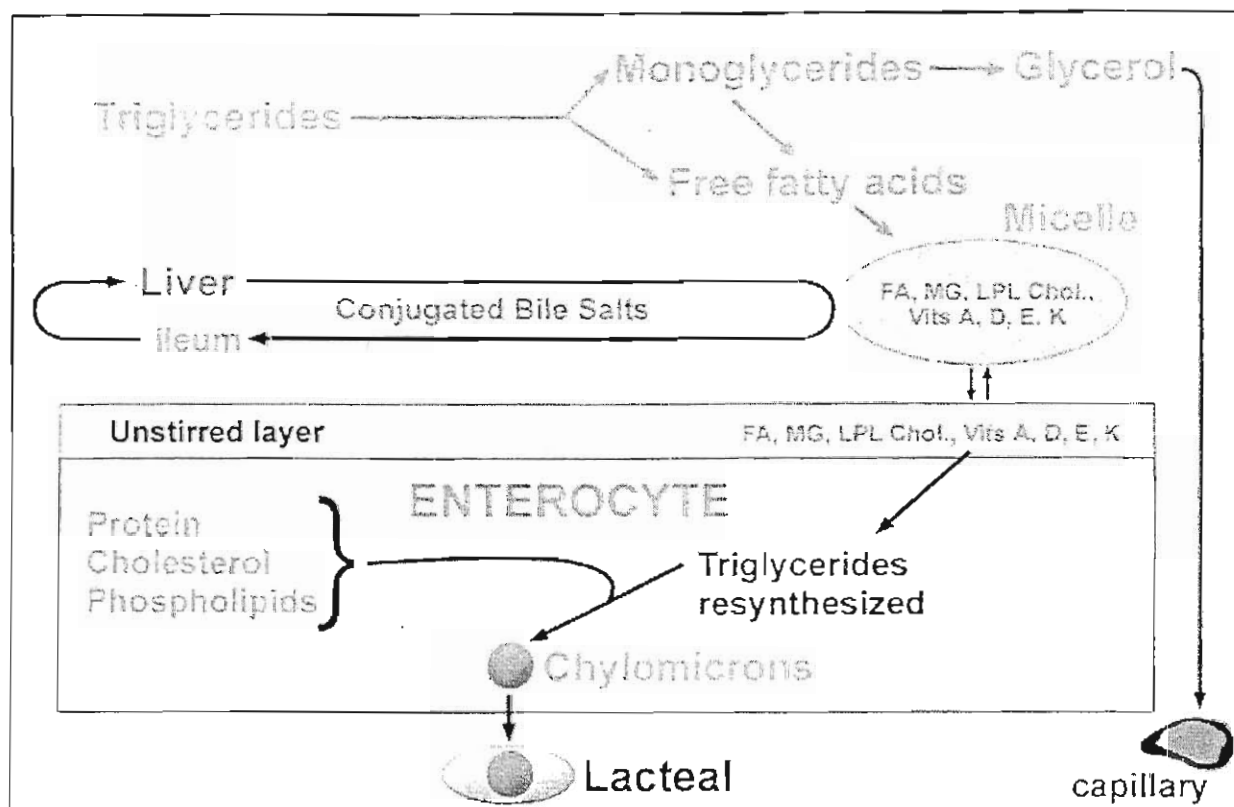
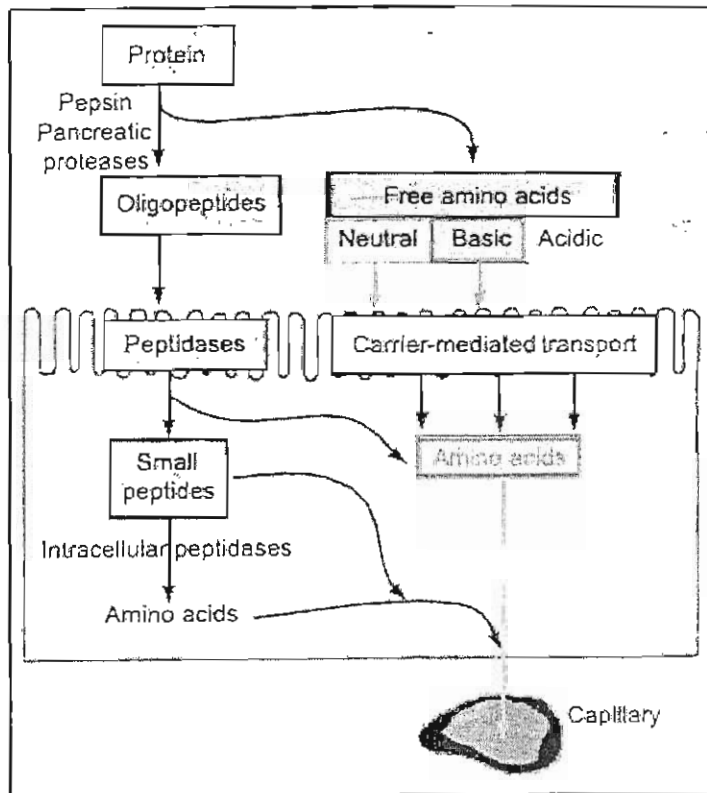
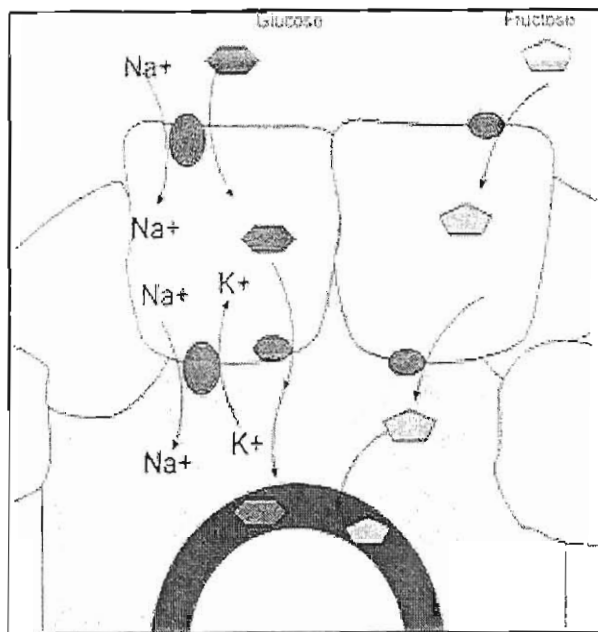
### Absorption:

Micelles formation (With bile salts)  
 Short & medium-chain FA are absorbed through the portal vein  
 Long-chain FA are absorbed through the lacteals (Chylomicrons)



## D) Minerals

- Calcium: }
- Phosphate: }
- Iron: }
- Vitamin B12: }
- Sodium: }
- Potassium: }



# Investigations of Malabsorption

## Absorptive Function

### A) Carbohydrate malabsorption

1. Stool pH < 5.6
2. Clinitest: For detection of unabsorbed reducing sugars "*Color change*"  
NB: Lactose & maltose are reducing  
Sucrose is **not** a reducing sugar & requires hydrolysis to become reducing sugar
3. Plasma glucose concentration: Fasting & after oral glucose "as in OGTT"  
- In CHO malabsorption, plasma glucose does not  $\uparrow\uparrow > 50 \text{ mg\%}$
4. Hydrogen breath test  
- Measurement of  $\text{H}_2$  in expired air after CHO intake (1-2 g/Kg)  
- Unabsorbed sugars are fermented by normal bacterial flora  
- In CHO malabsorption,  $\uparrow\uparrow \text{H}_2$  in expired air ( $> 20$  parts per million)  
- **False -Ve results:** Antibiotics & individuals who don't have  $\text{H}_2$  producing flora
5. Small bowel mucosal biopsy: For measurement of Lactase, Maltase & Sucrase conc.  
- In **primary** enzyme deficiency:  $\downarrow\downarrow$  Enzyme + Normal mucosal morphology  
- In **secondary** "*Partial or total villous atrophy*":  $\downarrow\downarrow$  Enzyme + Abnormal mucosa
6. Stool osmolality & ion gap:  
- In CHO malabsorption:  $\uparrow\uparrow$  Osmolality & Ion gap

### B) Protein malabsorption

1. Serum albumin
2. Stool  $\alpha_1$ -antitrypsin:  $\uparrow\uparrow$  in protein-losing enteropathy
3.  $\text{Cr}^{51}$  labeled albumin

**$\alpha_1$ -AT:** Serum protein  
Resistant to digestion

### C) Fat malabsorption

1. Stool fat globules: Sudan stain
2. Quantitative stool fat excretion: 3-day stool collection
3. Fasting serum carotene
4. Serum level of fat-soluble vitamins A, D, E
5. Prothrombin time (Vitamin K)

$$\text{Coefficient of fat absorption} = \frac{\text{Fat intake} - \text{fat loss}}{\text{Fat intake}} \%$$

### D) Mineral & Vitamin malabsorption

1. Schilling test: Vitamin  $\text{B}_{12}$  malabsorption
2. Serum level of iron, Ca, Mg, vitamins

### E) Pancreatic exocrine function

1. Sweat chloride test
2. Stool elastase:  $\downarrow\downarrow$  in pancreatic dysfunction (False +Ve result in watery diarrhea, why?)
3. Serum trypsinogen
4. Direct analysis of duodenal aspirate: For lipase, trypsinogen... [Gold standard test]

# Other Investigations

## **A)Hematologic**

1. Microcytic hypochromic anemia: Iron deficiency
2. Macrocytic anemia: Folic & vitamin B<sub>12</sub> deficiency
3. Acanthocytes: Abetalipoproteinemia
4. Neutropenia: Shwachmann-Diamond

**Multiple biopsies should be taken, why?**

## **B)Small bowel mucosal biopsy**

1. Mucosal lesions: Mucosal lesions (celiac, intestinal lymphangiectasia...)
2. Mucosal disaccharidases activity
3. PAS for microvillus inclusion disease

## **C)Microbiologic**

1. Giardiasis: Duodenal aspirate, stool analysis (for cysts), serology (serum antibodies)
2. Bacterial culture: of upper small intestine
3. AIDS: Chronic diarrhea & FTT may be the first presentation of AIDS

## **D)Imaging**

1. X-ray abdomen:
2. Barium:
3. US: Liver, biliary system, pancreas
4. ERCP: biliary system, pancreas

**Initial Work-up of a case with suspected malabsorption:**

- 
- 
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# Disorders of Malabsorption

## Definition

- ↓↓ Intestinal absorption of one or more dietary nutrients
- It may be due to defect in digestion or intestinal absorption
- Almost all causes are accompanied by diarrhea

Diarrhea is the main clinical expression of malabsorption

## Clinical Picture

- A) FTT, Loss of weight: Growth curves
- B) Muscle wasting
- C) Loss of SC fat: Thin wrinkled skin with marked bony prominences
- D) Edema: Protein-losing enteropathy
- E) Vitamin deficiency:
  - Vitamin A: Keratomalacia, xerophthalmia, blindness, bitot spots, infections
  - Vitamin K: Bleeding (Hypoprothrombinemia)
  - Vitamin D: Rickets
  - Vitamin E: Peripheral neuropathy
  - Vitamin B<sub>1</sub>: Beri-Beri
  - Vitamin B<sub>2</sub>: Stomatitis & glossitis
  - Vitamin B<sub>6</sub>: Peripheral neuropathy
  - Vitamin B<sub>12</sub>: Megaloblastic anemia
  - Vitamin C: Scurvy
  - Folic acid: Megaloblastic anemia
- F) Mineral deficiency:
  - Iron deficiency anemia
  - Hypocalcemia
  - Zinc deficiency: Acrodermatitis enteropathica "Perioral & perianal rash"
  - Copper deficiency: Menkes syndrome "Abnormal hair"
- G) Dehydration
- H) Hypoglycemia
- I) Clubbing: Celiac disease & cystic fibrosis
- J) Picture of the cause

### Diarrhea in malabsorption

- Watery explosive: CHO
- Bulky loose: Celiac disease
- Offensive pasty: Exocrine pancreas

## Etiology

### I) Neonatal Diarrhea

Condition	C/P
Microvillus inclusion disease	Watery diarrhea
Tufting enteropathy	
Congenital glu.-gal. malabsorption	Acidic stools
Congenital lactase deficiency	
Congenital Cl diarrhea	Polyhydramnios, watery diarrhea, metabolic alkalosis
Congenital Na diarrhea	Polyhydramnios, watery diarrhea
Congenital bile acid malabsorption	Steatorrhea
Congenital lipase deficiency	
Congenital enterokinase deficiency	FTT & edema
Congenital trypsinogen deficiency	
Enteric anendocrinosis	FTT & acidosis

## II) Classification according to the predominant nutrient malabsorbed

### A. CHO malabsorption

1. Lactose malabsorption (Congenital, Hypolactasia, Secondary lactase deficiency)
2. Congenital sucrase-isomaltase deficiency
3. Glucose-galactose malabsorption

### B. Fat malabsorption

1. Pancreatic exocrine insufficiency
  - Cystic fibrosis
  - Shwachman-Diamond syndrome
  - Chronic pancreatitis
  - Pearson syndrome
  - Protein-calorie malnutrition
2. Liver and biliary disorders
  - Cholestatic liver disease
  - Bile acid synthetic defects
3. Abetalipoproteinemia
4. Hypobetalipoproteinemia
5. Chylomicron retention disease (Anderson disease)
6. Acid lipase deficiency (Wolman disease)
7. Congenital bile acid malabsorption
8. Terminal ileal disease
9. Trypsinogen and enterokinase deficiency
10. Lymphangiectasia

### C. Amino acid malabsorption

1. Lysinuric protein Intolerance (defect in dibasic amino acid transport)
2. Hartnup disease (defect in free neutral amino acids including tryptophan)
3. Blue diaper syndrome (isolated tryptophan malabsorption)
4. Methionine malabsorption

### D. Mineral & vitamin malabsorption

1. Congenital chloride diarrhea
2. Congenital sodium diarrhea
3. Acrodermatitis enteropathica (Zinc malabsorption)
4. Menke disease (copper malabsorption)
5. Vitamin-D dependent rickets
6. Folic acid malabsorption
7. Vitamin B<sub>12</sub> malabsorption
8. Primary hypomagnesemia

### E. Drug-induced

1. Sulfasalazine: Folic acid deficiency
2. Phenytoin: Vitamin D & Ca deficiency
3. Cholestyramine: Ca & fat malabsorption



### III) Generalized Malabsorption states (Mucosal Defects)

1. Pancreatic exocrine insufficiency "*Mention causes*"
2. Liver & biliary disorders "*Mention causes*"
3. Celiac disease
4. Cow's milk protein enteropathy
5. Congenital microvillus atrophy, Tufting enteropathy & Enteric anendocrinosis
6. Short bowel syndrome
7. Stagnant loop syndrome: Bacterial overgrowth
8. Eosinophilic enteropathy
9. Protein-losing enteropathy: "*Mention causes; lymphangiectasia...*"
10. Intestinal infection: Giardia, cryptosporidium, Rota virus,  
Shigella, Salmonella, Campylobacter  
Postinfectious enteropathy  
Tropical sprue, Whipple [*Tropheryma whipplei*]
11. Immunodeficiency (1ry or 2ry) "*Mention causes*"
12. Immunoproliferative small intestinal disease: Variant of MALT lymphoma
13. Autoimmune enteropathy (IPEX)
14. Radiation enteritis

## **Celiac Disease**

(Gluten-Sensitive enteropathy)

### Definition

Immune-mediated enteropathy caused by permanent sensitivity to **gluten-containing cereals** as wheat, rye & barley in **genetically** predisposed individuals

### Incidence

- 1:100
- Underestimated (Undiagnosed: Diagnosed ratio is 7:1!!)
- Higher frequency in children with Down, Turner, type 1 DM, selective IgA deficiency

### Etiology

#### 1. Genetic predisposition:

- Concordance rate in monozygotic twins is 80-100% & in DZT is 20%
- HLA association: HLA-DQ2 in 95% of cases & DQ8 in the remainder
- Non-HLA genes: Risk is ↑↑ in certain genes (some are shared with type 1 DM)

#### 2. Environmental

- Dietary exposure: Wheat (gliadin), rye (secalin) or barley (hordeins)
- Viral infection: Rota virus

### Pathology

- Site: Mainly in the proximal small bowel
- Nature: Villous atrophy, crypt hyperplasia, epithelial damage & lymphocytic infiltration

### Pathogenesis

- Celiac disease develops only after dietary exposure to gluten
- Celiac disease is T-cell mediated chronic inflammatory disorder
- Altered processing by intestinal enzymes & intestinal permeability may be involved
- Cytokines: IFN- $\gamma$ , IFN- $\alpha$ , IL-15, IL-18

## Clinical Picture

- Onset: 6-24 months
- Variable presentation, but typical presentation: FTT + Diarrhea + Abdominal distension
- Clinical spectrum (**Celiac iceberg**)

Symptomatic
▪ C/P of celiac
Silent
<ul style="list-style-type: none"> <li>▪ No symptoms + Abnormal histologic (villous atrophy)</li> <li>▪ Identified by serologic screening in at-risk groups</li> </ul>
Latent
<ul style="list-style-type: none"> <li>▪ Normal histology (Now)</li> <li>▪ But at some other time, before or after, have shown a gluten-dependent enteropathy</li> </ul>
Potential
<ul style="list-style-type: none"> <li>▪ Positive serology</li> <li>▪ Normal histology</li> <li>▪ F/U is important, why?</li> </ul>

### - Other manifestations:

System	Manifestations
GIT	Anorexia, Diarrhea, Vomiting (Occasionally; constipation) Abdominal distension Weight loss, FTT, edema Aphthous stomatitis
Hematologic	Anemia (Iron deficiency)
Skeletal	Rickets, Osteoporosis, clubing Enamel hypoplasia of the teeth
Neurologic	Peripheral neuropathy Muscle atrophy Epilepsy Irritability
Endocrinologic	Short stature Delayed puberty Secondary hyperparathyroidism
Dermatologic	Dermatitis herpetiformis ( <i>Blisters, not caused by herpes</i> ) Alopecia areata Erythema nodosum
Respiratory	Idiopathic pulmonary hemosiderosis

### - Associated disorders:

- Syndromes: Down, Turner, Williams
- Autoimmunity: Type 1 DM, thyroiditis, Addison disease, autoimmune cholangitis, autoimmune hepatitis, Iry biliary cirrhosis, IgA nephropathy, dilated cardiomyopathy, Sjögren syndrome, alopecia, arthritis
- Selective IgA deficiency (present in 2%, 10-fold > general population)

## Screening & Diagnosis

### A) Serology (Antibodies)

- ☒ Anti-tissue transglutaminase IgA (TG2): Sensitivity (87%) & specificity (95%)
  - ☒ Anti-endomysium IgA & IgG
  - ☒ Anti-gliadin IgA
  - ☒ Anti-reticulin IgA
- } No longer recommended

- False negative results of Anti-tissue transglutaminase IgA & Anti-endomysium IgA occurs in patients with IgA deficiency which is associated with ↑ incidence of celiac disease
- Measurement of serum IgA is mandatory
- Reversal of positive serologic tests after gluten-free diet is a supportive evidence

### B) Small intestinal biopsy

- ☒ Definitive diagnosis (Gold standard)
- ☒ Pathology
- ☒ Re-biopsy after GFD is indicated only if there is equivocal clinical response to diet
- ☒ Gluten challenge is & re-biopsy may be needed in doubtful cases
- ☒ In children < 2 yrs, 2-3 biopsies may be needed
  - 1<sup>st</sup>: For diagnosis
  - 2<sup>nd</sup>: For documentation of healing after gluten-free diet
  - 3<sup>rd</sup>: To show recurrent damage with reintroduction of gluten

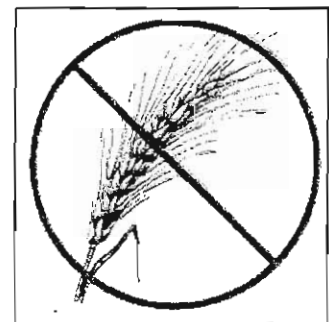
- Mucosal involvement may be patchy
- Multiple biopsies must be obtained

### C) Genetic diagnosis

- ☒ Measurement of HLA-DQ2 & 8
- ☒ It is good negative test (Exclusion of celiac disease)

## Treatment

- Life-long exclusion of gluten is the only treatment (Wheat, rye, barley). Oat is allowed
- Advantages:
  - Reversal of growth failure
  - Improvement of symptoms
  - Improvement of bone mineralization
  - ↓↓ Risk of malignancy
  - Compliance can be monitored by tTG (specially in adolescents)



## Prognosis

- Good response to gluten-free diet "Mention"
- Risk of malignancy: Intestinal lymphoma & other forms of cancer
- The main cause of death is non-Hodgkin lymphoma

## DD of flat mucosa

- |                        |                          |                                |
|------------------------|--------------------------|--------------------------------|
| ▪ Bacterial overgrowth | ▪ Celiac disease         | ▪ Autoimmune enteropathy       |
| ▪ Giardiasis           | ▪ Cow's milk enteropathy | ▪ Eosinophilic gastroenteritis |
| ▪ HIV enteropathy      | ▪ Crohn disease          | ▪ Protein energy malnutrition  |
| ▪ Immunodeficiency     | ▪ Tropical sprue         | ▪ Lymphoma                     |
| ▪ GVHD                 | ▪ Tuberculosis           | ▪ Chemotherapy and radiation   |

# Short Bowel Syndrome

## Definition

Loss of > 50 % of small intestine ( $\pm$  portion of the large intestine)

## General Background

- At birth, length of small intestine = 200-250 cm
  - In adults, length of small intestine = 300-800 cm
  - However, bowel resection in infants has better prognosis?
  - Infant with 15 cm small intestine with ileocecal valve
  - Infant with 20 cm small intestine without ileocecal valve
- } Has survival potential

## Etiology

Congenital	Acquired (Resection)
Congenital short bowel syndrome	NEC
Multiple atresias	Crohn disease
Gastroschisis	Long segment Hirschsprung disease
	Meconium peritonitis
	Intussusception, volvulus

## Pathophysiology

- $\downarrow\downarrow$  Length  $\Rightarrow$   $\downarrow\downarrow$  Surface area for absorption
- Normally, vitamin B<sub>12</sub> & bile salts are absorbed only in the distal ileum
- Loss of bile acids  $\Rightarrow$  Fat malabsorption
- $\uparrow\uparrow$  Bile salts delivery to the colon  $\Rightarrow$  Irritation with  $\uparrow\uparrow$  water & electrolyte secretion
- Jejunal resection is tolerated better than ileal resection
- Loss of the ileocecal valve  $\Rightarrow$   $\downarrow\downarrow$  Time of contact of nutrients with mucosa  
 $\uparrow\uparrow$  Retrograde flow of colonic bacteria

## Clinical Picture

- Diarrhea, malabsorption, FTT & weight loss

## Clinical Picture

- Secondary hyperoxaluria: Renal stones
- GB stones
- Complications of TPN "Mention"

## Treatment

### 1. Nutrition

- ☒ TPN (Central lines are usually needed)
- ☒ Small frequent feeds or
- ☒ Continuous NGT infusion
- ☒ Type of enteral feeding: Breast milk or elemental formula (protein hydrolysate & medium-chain TG)

### 2. Vitamin supplementation

### 3. Electrolyte supplementation

### 4. Rx of bacterial overgrowth: Oral metronidazole

### 5. Drugs:

- ☒ Loperamide :  $\downarrow\downarrow$  Gut motility
- ☒ Cholestyramine (BA sequestrant): binds bile & prevent its reabsorption

### 6. Small bowel transplantation

### 7. Other lines: Intestinal growth factors, lengthening procedures...

# **Protein-Losing Enteropathy**

## **Definition**

Conditions leading to excess intestinal protein loss

## **Etiology**

### **A) Intestinal lymphangiectasia**

#### **a. Primary intestinal lymphangiectasia**

- ☒ Turner, Noonan
- ☒ Klippel-Trenaunay syndrome

#### **b. Secondary intestinal lymphangiectasia**

- ☒ Constrictive pericarditis
- ☒ Congestive HF
- ☒ Post-Fontan procedure
- ☒ Tumors
- ☒ Trauma

### **B) Bowel mucosal inflammation**

#### **a. Infection**

- ☒ Bacterial overgrowth
- ☒ CMV infection
- ☒ Giardia

#### **b. Gastric inflammation**

- ☒ Eosinophilic GE
- ☒ Congestive HF

#### **c. Intestinal inflammation**

- ☒ Celiac disease
- ☒ Crohn disease
- ☒ Tropical sprue
- ☒ Radiation enteritis

#### **d. Colonic inflammation**

- ☒ NEC
- ☒ IBD

## **Intestinal Lymphangiectasia**

- Obstruction of the intestinal lymphatic drainage
- Leakage of the lymph into the bowel lumen & peritoneal cavity
- Lymph is rich in proteins & lymphocytes
  - Protein-losing enteropathy, hypoalbuminemia
  - Lymphopenia, hypogammaglobulinemia
  - Edema, chylous ascites
- Investigations
  - ↑↑ Stool  $\alpha_1$ -antitrypsin
  - Small bowel mucosal biopsy: Dilated lacteals
  - Blood investigations: *Mention*
  - Paracentesis after fat-containing meal: Milky fluid with ↑↑ TG, lymphocytes & protein
- Treatment
  - Diet: Medium-chain TG (MCTs)
  - Surgery may be indicated in localized intestinal lesions

# Intestinal Infection & Malabsorption

## Stagnant Bowel Syndrome

(Bacterial overgrowth = Blind loop syndrome)

### Definition

Excessive number of bacterial in the small intestine or the stomach

### General Background

- Normally, the colon contains a large number of bacteria
- These bacteria have **symbiotic** relationship with the host:
  - Production of nutrients e.g., vitamin K...
  - Protection against pathogenic microorganisms
- Normally, the upper part of the small intestine is sterile, why?
  - Acidic gastric pH
  - Intestinal motility
  - Ileocecal valve: prevents colonic bacterial from entering the ileum
  - Mucosal defense mechanisms: Mucins & immunoglobulins

### Etiology

- Motility disorders: Scleroderma, pseudoobstruction...
- Congenital disorders: Duplication, malrotation, bands, diverticuli...
- Partial intestinal obstruction: adhesions...
- Short bowel syndrome
- Prematurity, immunodeficiency, malnutrition

### Pathophysiology [= Effects of Bacteria overgrowth]

- Deconjugation of bile salts → Steatorrhea (Fat malabsorption)
- Binding of vitamin B<sub>12</sub> → Anemia
- Villous atrophy → Diarrhea

### Investigations

1. Small intestinal aspirate: Culture & sensitivity
2. CHO malabsorption tests: *Mention*

### Treatment

1. Oral antibiotics: Mainstay of therapy
  - ☑ Metronidazole: 2-4 wks
  - ☑ Cycling of antibiotics: azithromycin, TMP-SMX, ciprofloxacin & metronidazole
  - ☑ Oral aminoglycosides: Gentamycin "Non-absorbable" may be used
2. Treatment of the cause

## Tropical Sprue

### Etiology

- Unknown. Infectious etiology is suspected
- It follows acute diarrheal disease & improves with antibiotic therapy

### Clinical Picture

- Acute phase: Fever, malaise, watery diarrhea
- Chronic phase: Malabsorption

### Investigations Biopsy (Villous atrophy)

### Treatment Oral folic acid and tetracyclin or sulfonamide

# Immunodeficiency Disorders

## Etiology

1. Congenital immunodeficiency: Bruton, selective IgA deficiency; CVID, SCID...
2. Secondary immunodeficiency: HIV infection, immunosuppressive therapy, nephrotic...

## Pathophysiology

- Malabsorption occurs with immunodeficiency disorders
  - Chronic infection: Giardiasis, Rota virus
  - Bacterial overgrowth
  - Opportunistic infections: CMV, Mycobacteria, Candida, Cryptosporidium

## Clinical Picture

- Picture of the cause
- Malabsorption

## Investigations & Treatment

# Autoimmune Enteropathy

## Etiology

- Autoimmune

## Clinical Picture

- Malabsorption, diarrhea, FTT
- Extra-intestinal manifestations: arthritis, IDDM, hypothyroidism, membranous GN, hemolytic anemia, thrombocytopenia, autoimmune hepatitis
- IPEX syndrome

## Investigations

- Endoscopy & biopsy: Villous atrophy crypt hyperplasia & chronic inflammatory cells
- Serum anti-enterocyte antibodies

## Treatment

- Immunosuppressives: Steroids, azathioprine, cyclophosphamide, cyclosporin
- IPEX: BM transplantation

# Phenotypic Diarrhea

(Tricho-hepato-enteric syndrome: THE syndrome)

## Etiology AR disease

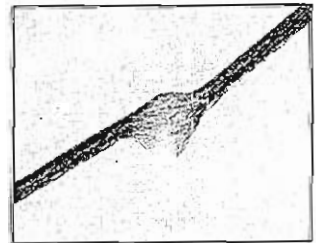
## Clinical Picture

- Tricho-: Trichorrhexis nodosa (woolly, easily detached, poorly pigmented)
- Hepato-: Fibrosis
- Enteric: Malabsorption, diarrhea, FTT
- Phenotypic: Dysmorphism, prominent forehead, hypertelorism, broad nose

## Investigations

- Endoscopy & biopsy: Non-specific villous atrophy

## Prognosis Death at the age 2-5 yrs



## **Bile Acid Malabsorption**

### **Etiology**

- Primary (Congenital): Mutation of ileal Na-Bile acid cotransporter gene
- Secondary (Acquired): Ileal disease & ileal resection

### **Pathophysiology & C/P**

- Normally, bile salts are absorbed only in the distal ileum (EHC)
- Loss of bile acids  $\Rightarrow$  Fat malabsorption (Ssteatorrhea)
- $\uparrow\uparrow$  Bile salts delivery to the colon  $\Rightarrow$  Irritation with  $\uparrow\uparrow$  water & electrolyte secretion
- Neonatal diarrhea, malabsorption, FTT

### **Treatment**

- Chenodeoxycholic acid

## **Abetalipoproteinemia**

## **Hypobetalipoproteinemia**

## **Chylomicron Retention Disease**

## **Wolman Disease**

**Etiology** Acid lipase deficiency (AR)  $\rightarrow$  Accumulation of cholesterol esters

**Clinical Picture** FTT + Steatorrhea + HSM + Calcification of the adrenal glands

## **Immunoproliferative Small Intestinal Disease**

### **Etiology**

- Intestinal malignant lymphoma: Burkitt, Non-Hodgkin, Mediterranean lymphoma
- Mediterranean lymphoma is now called IPSID (Variant of MALT lymphoma)

### **Clinical Picture**

- Diarrhea, malabsorption, abdominal pain, abdominal mass
- Intestinal obstruction

### **Investigations**

- Endoscopy & biopsy: Diffuse lesion usually in the proximal bowel
- Serum marker (IgA heavy chain)

### **Treatment**

- Early IPSID: Antibiotics
- Lymphoma: Chemotherapy



# **Congenital Intestinal Mucosal Defects**

## **Microvillus inclusion disease**

(Congenital Microvillus Atrophy)

### **Etiology**

- Autosomal recessive
- Most common cause of congenital diarrhea →

### **Clinical Picture**

- At birth: Profuse watery secretory diarrhea
- Dehydration, FTT

### **Pathology**

- Villous atrophy with no inflammatory infiltrate
- Positive PAS inclusions
- E/M: Microvilli within invaginations of the apical membrane

### **Investigations**

- Endoscopy & biopsy

### **Treatment**

- TPN
- Somatostatin analogs: Octreotide
- Intestinal transplantation: is the only definitive treatment

### **Neonatal Diarrhea:**

- Microvillus inclusion disease
- Tufting enteropathy
- Congenital glu.-gal. malabsorption
- Congenital lactase deficiency
- Congenital Cl diarrhea
- Congenital Na diarrhea
- Congenital bile acid malabsorption
- Congenital lipase deficiency
- Congenital enterokinase deficiency
- Congenital trypsinogen deficiency
- Enteric anendocrinosis

## **Tufting Enteropathy**

(Intestinal epithelial dysplasia)

**Etiology** Disorders of cell-cell & cell matrix interaction

### **Clinical Picture**

- First weeks of life (Typically, Not at birth): Persistent watery diarrhea

### **Pathology**

- Focal epithelial tufts (teardrop-shaped groups of enterocytes)

**Investigations & Treatment** As microvillus inclusion disease

## **Enteric Anendocrinosis**

(Intestinal epithelial dysplasia)

**Etiology** Mutation of NEUROG3

### **Clinical Picture**

- Vomiting, diarrhea, acidosis

### **Pathology**

- Normal villus-crypt architecture
- Staining of neuroendocrine cells: Negative

**Investigations & Treatment** As microvillus inclusion disease

# Enzyme Deficiencies

## Classification

1. CHO malabsorption: Lactase deficiency, Sucrose\_Isomaltase deficiency, Glucose-Galactose & Fructose malabsorption
2. Exocrine pancreatic insufficiency: Mention causes (*CF is the commonest*; including Trypsinogen and enterokinase deficiency)

	Lactase Deficiency (Lactose intolerance)	Sucrose-Isomaltase Deficiency	Glucose-Galactose malabsorption
Etiology	<ul style="list-style-type: none"> <li>• Congenital Lactase ↓↓: Very rare</li> <li>• Primary adult type hypolactasia: caused by physiological ↓↓ in lactase with age (More in blacks)</li> <li>• Secondary lactose intolerance: Mucosal damage (GE)</li> </ul>	<ul style="list-style-type: none"> <li>• AR<sup>3</sup></li> <li>• ↓↓ Sucrose_Isomaltase enzyme</li> </ul>	<ul style="list-style-type: none"> <li>• AR (&gt; 30 known mutations)</li> <li>• SGLT1 gene</li> <li>• Glucose &amp; galactose/Na cotransport system</li> </ul>
Clinical Picture			
a. General features of CHO malabsorption	<input checked="" type="checkbox"/> Loose watery diarrhea <input checked="" type="checkbox"/> Flatulence & abdominal distention <input checked="" type="checkbox"/> Abdominal pain & discomfort		
b. Specific features	<input checked="" type="checkbox"/> Most common	<input checked="" type="checkbox"/> Onset after exposure to sucrose (Fruits & sweets)	
Investigations			
a. General features	<input checked="" type="checkbox"/> Stool pH: acidic <input checked="" type="checkbox"/> Stool reducing sugars <input checked="" type="checkbox"/> H <sub>2</sub> breath test		
b. Specific features		<input checked="" type="checkbox"/> Acid hydrolysis of stool, why?	<input checked="" type="checkbox"/> Prenatal genetic diagnosis is available
Treatment			
	Lactose-free formula (or diet)	Sucrose-free formula (or diet)	The only allowed sugar is fructose

# Defects of Absorption or Transport

## Classification

1. Amino acid transport defects
2. Disorders of vitamin absorption
  - Vitamin B<sub>12</sub> malabsorption
  - Congenital malabsorption of folic acid
  - Vitamin D dependent rickets
3. Disorders of mineral absorption
  - Congenital Chloride diarrhea
  - Congenital Na diarrhea
  - Primary hypomagnesemia
  - Acrodermatitis enteropathica
  - Menkes syndrome (Kinky hair)

Congenital Chloride diarrhea	Congenital Na diarrhea	Primary hypomagnesemia	Amino acid transport defects
<ul style="list-style-type: none"> <li>- Etiology: AR</li> <li>- Defect: Defective Cl/HCO<sub>3</sub> transport</li> <li>- C/P: Watery diarrhea polyhydramnios</li> <li>- Lab.: ↓↓ Cl, ↓↓ K, Alkalosis ↑↑ Stool Cl</li> <li>- Rx: Supportive</li> </ul>	<ul style="list-style-type: none"> <li>- Defect: Defective Na/H exchange</li> <li>- C/P: Watery diarrhea polyhydramnios</li> <li>- Lab.: Acidosis ↑↑ Stool Na</li> <li>- Rx: Supportive (ORS)</li> </ul>	<ul style="list-style-type: none"> <li>- Defect: Defective Mg absorption</li> <li>- C/P: Neonatal seizure Tetany</li> <li>- Lab.: ↓↓ Mg, ↓↓ Ca</li> <li>- Rx: Mg supplementation</li> </ul>	<ol style="list-style-type: none"> <li>1. Lysinuric protein Intolerance (defect in dibasic aa transport)</li> <li>2. Hartnup disease (defect in tryptophan absorption)</li> <li>3. Blue diaper syndrome (isolated tryptophan malabsorption)</li> <li>4. Methionine malabsorption</li> </ol>
Acrodermatitis enteropathica	Menkes syndrome (Kinky hair)	Vitamin D dependent Rickets	Vitamin B <sub>12</sub> & Congenital folic acid malabsorption
<ul style="list-style-type: none"> <li>- Etiology: AR</li> <li>- Defect: Defective Zinc absorption</li> <li>- C/P: Circumoral &amp; perianal rash Alopecia, chronic diarrhea</li> <li>- Lab.: ↓↓ Zn, ↓↓ ALP</li> <li>- Rx: Oral Zn (1-2 mg/Kg/day)</li> </ul>	<ul style="list-style-type: none"> <li>- Etiology: XLR</li> <li>- Defect: Defective Cu absorption</li> <li>- C/P: Cerebellar degeneration Hypotonia, Abnormal hair</li> <li>- Lab.: ↓↓ Cu, MRI brain</li> <li>- Rx: Parenteral copper</li> </ul>	<ul style="list-style-type: none"> <li>- Etiology: AR</li> <li>- Defect: Defective Ca absorption</li> <li>- C/P: Rickets</li> <li>- Lab.: ↓↓ Ca, N or ↓↓ P, ↑↑ ALP</li> <li>- Rx: Vitamin D (active form high dose)</li> </ul>	See Hematology

# Peptic Ulcer Disease

## Definition

- Deep mucosal lesions that disrupt the *muscularis mucosa* (due to action of HCl & pepsin)
- More often duodenal than gastric

## Classification

### a. Primary: Chronic & more often duodenal

- Usually associated with *H. pylori* infection
- Idiopathic (15%): High recurrence rate

25% of critically ill children in PICUs have gastric bleeding

### b. Secondary: Acute & more often gastric

- Stress, shock
- IC lesion (Cushing ulcer), severe burn (Curling ulcer)
- Drugs: Steroids, aspirin, NSAIDs [*Direct & indirect, how?*]
- Neuroendocrinal tumors (NET): Gastrinoma, Zollinger-Ellison, mastocytosis
- Crohn disease (affecting stomach or duodenum)
- Tumors, radiation damage
- Viral infection: CMV, HSV

## Pathogenesis

### a. Acid secretion:

- Parietal cells secrete HCl & IF
- HCl secretion is ↑↑ by: Gastrin, vagal stimulation, histamine

### b. Mucosal defense:

- Mucus secretion is ↑↑ by PG<sub>2</sub>
- Epithelial tight junctions

## Clinical Picture

- Epigastric pain (*Dull aching*), worse at night
- Nausea, vomiting
- Bleeding (50%)
- Iron deficiency anemia
- Acute abdominal pain with perforation or pancreatitis

Classically (But uncommon): Food  
Relieves pain in DU & exacerbates pain in GU

## Investigations

- Endoscopy
- Biopsy specimes should be taken from esophagus, stomach & duodenum, why??
- Investigation of *H. pylori*
  - Biopsy: Histology, rapid urease test & culture
  - Blood antibody test
  - Stool antigen test
  - Urea breath test (based on the ability of *H. pylori* to convert urea to NH<sub>3</sub> & CO<sub>2</sub>)

## **Helicobacter pylori**

**Microbiology:** Helix-shaped, Gram-negative, urease-producing bacterium

**Mode of transmission:** Ingestion

**Manifestations:**

- 80 % of infected individuals are clinically asymptomatic (**But should be treated**)
- Chronic gastritis, DU, GU, stomach cancer
- **Extra-gastric** manifestations: Anemia, ITP, short stature, SIDS

## Treatment

### A) Active GIT bleeding

1. Stabilization of the patient [A, B, C]
2. Monitoring of vital signs & Hct
3. Vascular access + Fluid therapy (Shock therapy)
4. Blood transfusion
5. NGT: for monitoring of bleeding
6. Drugs:
  - o PPI (Omeprazole may be used)
  - o H<sub>2</sub> blockers (Ranitidine or Cimetidine)
7. Endoscopy
  - Diagnostic: Bleeding site
  - Therapeutic: Stop bleeding (pressure, laser coagulation, adrenaline injection or clips)

### B) Peptic ulcer without active bleeding

1. Goals: Ulcer healing, relief of symptoms & prevention of complications
2. Drugs used: H<sub>2</sub> blockers, PPI ± Cytoprotective agents
3. Surgical Rx is rarely indicated (uncontrolled bleeding, perforation or obstruction)

Medications	Dose	Form
<b>H<sub>2</sub> receptor antagonists</b>		
Cimetidine	20-40 mg/kg/day in 2 divided doses	Tab (200 mg)
Ranitidine	4-10 mg/kg/day in 2 divided doses	Tab (150 mg)
Famotidine	1-2 mg/kg/day in 2 divided doses	Tab (20 mg)
Nizatidine	10 mg/kg/day in 2 divided doses	Tab (150 mg)
<b>Proton pump inhibitors</b>		
Omeprazole ( <i>Losec</i> )	1-3 mg/kg/day in 2 divided doses	Cap (20, 40 mg)
Lansoprazole ( <i>Lanzor</i> )	1-3 mg/kg/day in 2 divided doses	Cap (15, 30 mg)
Rabeprazole ( <i>Pariet</i> )		Cap (20 mg)
Pantoprazole ( <i>Controloc</i> )		Cap (20, 40 mg)
<b>Cytoprotective agents</b>		
Sucralfate	40-80 mg/kg/day	Tab (1 gm)

### C) Treatment of H. pylori-related PUD

Medications	Dose	Duration
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
<b>Or</b>		
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
<b>Or</b>		
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo

# Foreign Bodies in the Stomach

## Important Remarks

- 95% of FB in the stomach pass in the GIT without difficulty
- Areas of difficulty: Pylorus, IC valve, duodenal sweep, diverticula, previous bowel surgery
- Age: 6 m- 6yrs
- Coins are the commonest
- 90% of FB are radio-opaque
- Conservative management is indicated in most of FB passed into the stomach
  - Symptoms: Abdominal pain, vomiting, fever, bleeding
  - Usual duration: 4 days-4 wks
- As a rule (Children): FB > 5 cm diameter or 2 cm thickness should be removed
- As a rule (Infants): FB > 3 cm length should be endoscopically removed

FB	Risk	Management
Sharp or long objects	Perforation	Monitor radiologically
Straight pins	Perforation	Weekly assessment
Open safety pins	Perforation	Removal
Magnet (Single)	Minor problem	Conservative
Magnet (Multiple)	Bowel perforation & fistula, why?	Removal
Lead-containing materials	Lead poisoning	Removal & Lead level
Batteries (Ordinary)	↑↑ Risk of mercury poisoning & Electrical injury	Remove if large, remain in stomach > 48 hr or symptoms (N, V)
Batteries (Lithium)	Lithium toxicity	Remove immediately
Cocaine packing	Toxicity	Surgical removal

## Bezoar

### Definition

- Bezoar is accumulation of exogenous matter in the stomach or intestine
- Composition: Food, fiber, hair

### Etiology

- More common in females (2nd decade)
- Personality problems or neurologic impairment

### Classification

- a. Trichobezoars: Patient's own hair
- b. Phytobezoars: Plant & animal materials
- c. Lactobezoars: Milk (High casein or Ca content)
- d. Others: Chewing gum

### Clinical Picture

- Gastric or intestinal obstruction
- Abdominal pain, halitosis
- Malabsorption
- Examination: Abdominal mass, patch baldness

Investigations Abdominal X-ray, US, CT, Barium studies

Treatment Endoscopic or surgical removal (Lactobezoars usually resolve spontaneously)

# Inflammatory Bowel Disease

## Definition

Idiopathic chronic intestinal inflammation: 1. Crohn disease 2. Ulcerative colitis

## Etiology

A) Genetic: Family studies & certain HLA types

- Concordance rate in MZT is 36% in Crohn & 16% in ulcerative colitis
- Associations: Turner, GSD-Ib, Hermansky-Pudlak

B) Environmental:

- Smoking is a risk factor for Crohn disease (But protects against UC!)
- Infectious agents??

## Pathogenesis

- Normally, there is physiologic inflammation in response to microbial & dietary antigens
- Failure to check such response: Pathologic inflammation (Mediators; cytokines, O<sub>2</sub> radicals...)

## Differential Diagnosis

	Crohn	Ulcerative colitis
Transmural involvement	Common	
Skip lesions (Discontinuous)	Common	
Crypt abscess		Common
Granulomas	Common	
Linear ulcers		Common
Mouth ulcers (Aphthous)	Common	Rare
Stomach, esophagus	More common	No
Ileal disease	Common	No (Except backwash ileitis)
Colonic disease	50-75 %	100 %
Rectal disease ± bleeding	Occasional	Universal
Toxic megacolon	No	Yes
Fissure, Fistula, Stricture, Perianal disease	Common	
Abdominal pain & mass	Common	
Growth failure	Common (40%)	
Diarrhea, mucus, pus	Variable	Common
Risk for cancer	Increased	Greatly increased
pANCA	20%	70%
<b>Extra-intestinal</b>		
Renal stones	Common	
Gall stones	Common	
Arthritis	Common	
Episcleritis	Common	
Clubbing	Common	
Erythema nodosum	Common	
Pyoderma gangrenosum		Common
Ankylosing spondylitis		Common
Iry sclerosing cholangitis		Common
Chronic active hepatitis		Common
Cirrhosis		Common
<b>Both Diseases</b>	Uveitis, Conjunctivitis, Fatty liver, Cholangiocarcinoma	

# Inflammatory Bowel Disease

	Ulcerative Colitis	Crohn Disease
<b>Definition</b>	Idiopathic chronic inflammation of the colon Classically involve the rectum upwards It may be localized to the rectum (Ulcerative proctitis)	Idiopathic chronic inflammation of the bowel, involving any part from the mouth to the anus Classically involve the terminal ileum
<b>Incidence &amp; Age</b>	1-15:100.000 Median age at diagnosis: 12 yrs	5:100.000 (Increasing) Median age at diagnosis: 12 yrs
<b>Pathology</b>	<ul style="list-style-type: none"> <li>Site: Limited to rectum &amp; colon (NB: Backwash ileitis)</li> <li>Limited to the mucosa</li> <li>PNLs infiltration, cryptitis, crypt abscess</li> <li>Affection is extensive (Pancolitis in 60-80%)</li> </ul>	<ul style="list-style-type: none"> <li>Site: Any site from the mouth to the anus</li> <li>Transmural involvement but focal &amp; patchy (Skip areas)</li> <li>Non-caseating granuloma</li> <li>2/3 have affection of the terminal ileum &amp; Rt colon</li> </ul>
<b>Clinical Picture</b>	<ul style="list-style-type: none"> <li>Diarrhea with blood &amp; mucus</li> <li>Abdominal pain, tenesmus, cramps</li> <li>Fulminant colitis: Fever, anemia, leukocytosis, hypoalbuminemia, &gt; 5 bloody stools/day for &gt; 5 days</li> <li>Anemia, growth failure, weight loss: Less common</li> <li>Extraintestinal manifestations: Less common <i>See table</i></li> </ul>	<ul style="list-style-type: none"> <li>Presentation may be <b>subtle</b></li> <li><b>Classically (25%)</b>: Abdominal pain, diarrhea, weight loss</li> <li>Anemia, growth failure, weight loss, nutritional deficiencies</li> <li>Perianal disease: Anal pain, tags, abscess, fistula, fissure</li> <li>Extraintestinal manifestations: More common <i>See table</i></li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>CBC: anemia, leucocytosis (Severe colitis)</li> <li>ESR &amp; CRP: may be ↑↑</li> <li>Serum albumin, iron, Ca, Mg, Zn, folate, vitamin B<sub>12</sub></li> <li>pANCA: +ve in 70 %</li> <li>Plain X-ray: Dilatation in toxic megacolon</li> <li>Barium enema: Suggestive but not diagnostic Double contour with lead-pipe colon Smooth loss of colonic haustrations</li> <li>Colonoscopy &amp; biopsy: <ul style="list-style-type: none"> <li>Gross: Erythema, edema, friability, pseudopolyps</li> <li>Cutoff demarcation may be detected</li> </ul> </li> <li>Microscopic: <i>Pathology</i> <ul style="list-style-type: none"> <li>Contraindicated in fulminant colitis, why?</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>CBC: anemia, ± leucocytosis, thrombocytosis</li> <li>ESR: ↑↑</li> <li>Serum albumin, iron, Ca, Mg, Zn, folate, vitamin B<sub>12</sub></li> <li>pANCA: +ve in 20 %</li> <li>Anti-Saccharomyces cervisiae antibodies</li> <li>Anti-OmpC: Antibody to E. coli outer membrane porin</li> <li>Barium follow-through: Segmental distribution (Skip areas) Irregular mucosa, linear ulcers Strictures, fistulae...</li> <li>Radionuclide scan</li> <li>GIT endoscopy &amp; biopsy: <ul style="list-style-type: none"> <li>Gross: Erythema, edema, friability (Skip areas)</li> <li>Microscopic: <i>Pathology</i></li> </ul> </li> </ul>



Treatment	Aim: Relief of symptoms, induction of remission, prevention of complications & promotion of growth
<div> <input type="checkbox"/> Nutritional                 <input type="checkbox"/> Medical                 <input type="checkbox"/> Surgical                 <input type="checkbox"/> Psychological             </div>	<div> <b>Nutritional</b> <ul style="list-style-type: none"> <li>• High nutritive diet</li> <li>• Nutritional supplementation (Calorie, vitamins, minerals)</li> <li>• Exclusive enteral utritional therapy                             <ul style="list-style-type: none"> <li>➢ Elemental Unpalatable (NGT)</li> <li>➢ Polymeric: tolerated orally</li> </ul> </li> <li>• Remission rate: 86% (But short duration)</li> </ul> </div>
	<div> <b>Psychological &amp; family support</b> <ul style="list-style-type: none"> <li>• 5-Aminosalicylic acid (Sulfasalazine &amp; Mesalamine)                             <ul style="list-style-type: none"> <li>➢ Sulfasalazine: 50-75 mg/Kg/day (<i>Hyper sensitivity</i>)</li> <li>➢ Mesalamine: 50-75 mg/Kg/day (<i>Better tolerated</i>)</li> </ul> </li> <li>• 5-ASA: can be given as enema or suppositories (Proctitis)</li> <li>• Steroid enema: for proctitis</li> <li>• Steroid: Oral (1-2 mg/Kg/day) for 3-4 wks followed by tapering of the dose (IV steroids may be used in severe cases)</li> <li>• Immunomodulators: Azathioprine or 6-mercaptopurine used in steroid resistant or dependent colitis</li> <li>• Infliximab: Anti TNF-<math>\alpha</math></li> <li>• Surgery: "Total colectomy is curative"                             <ul style="list-style-type: none"> <li>➢ Intractable disease: Fulminant colitis not responding</li> <li>➢ Emergency: Perforation, bleeding</li> <li>➢ Carcinoma</li> </ul> </li> </ul> <b>NB: Pouchitis</b> (Common complication of surgery)                      - Rx: Oral metronidazole &amp; Probiotics                 </div>
<b>Prognosis</b>	<div> <ul style="list-style-type: none"> <li>• Remissions &amp; exacerbations</li> <li>• Most children will respond to medical Rx</li> <li>• <b>Fulminant colitis:</b> Perforation</li> <li>• Cancer colon                             <ul style="list-style-type: none"> <li>➢ Risk begins after 8-10 yrs of the disease</li> <li>➢ Annual colonoscopy &amp; biopsy (&gt; 10 yrs)</li> </ul> </li> <li>• Extraintestinal manifestations</li> </ul> </div>

## Extra-intestinal Complications of IBD

System	Manifestations
Hematologic	Anemia (↓↓ Iron, blood loss, ↓↓ Vitamin B <sub>12</sub> *, chronic inflammation) Autoimmune hemolytic anemia Anaphylactoid purpura (Crohn disease) Hyposplenism Coagulation abnormalities <ul style="list-style-type: none"> <li>• Increased activation of coagulation factors</li> <li>• Activated fibrinolysis</li> <li>• Anticardiolipin antibody</li> <li>• Thrombosis (Stroke, myocardial infarction, peripheral occlusions)</li> </ul>
Cardiac	Pleuropericarditis, Cardiomyopathy, Endocarditis, Myocarditis
Musculoskeletal	Arthritis (3 patterns) Clubbing, osteoporosis, osteomalacia
Endocrinologic	Growth failure, delayed sexual maturation, Thyroiditis
Neurologic	Peripheral neuropathy, Meningitis, Vestibular dysfunction Pseudotumor cerebri
Ocular	Conjunctivitis, Uveitis, iritis, Episcleritis, Scleritis, Crohn keratopathy
Dermatologic	Erythema nodosum, Pyoderma gangrenosum Epidermolysis bullosa acquisita Perianal skin tags, psoriasis
Hepatobiliary	Primary sclerosing cholangitis (PSC) Small duct PSC (pericholangitis) Carcinoma of the bile ducts Fatty infiltration of the liver Cholelithiasis Autoimmune hepatitis
Respiratory	Chronic bronchitis with bronchiectasis & neutrophilic infiltrates Fibrosing alveolitis Pulmonary vasculitis Bronchiolitis obliterans Eosinophilic lung disease Granulomatous lung disease Tracheal obstruction
Malnutrition	↓↓ Food intake (Dietary restriction) Malabsorption (IBD, Bowel resection, ↓↓ Bile salt, Bacterial overgrowth) Intestinal losses (Electrolytes, minerals, nutrients) Increased caloric needs (Fever, inflammation)
Renal	Renal amyloidosis, nephrotic syndrome Metabolic renal stones (uric acid, oxalate) Fibrosis (ureteric obstruction), Fistula formation
Pancreatitis	2ry to medications (sulfasalazine, 6-mercaptopurine, azathioprine, TPN) Granulomatous pancreatitis Ampullary Crohn disease Decreased pancreatic exocrine function Sclerosing cholangitis with pancreatitis

Vitamin B<sub>12</sub> deficiency is due to ileal disease or resection & bacterial overgrowth

## Important Remarks

- Extra-intestinal manifestations occur with CD > UC
- Joint, skin, eye, mouth, and hepatobiliary involvement occur with colitis (whether UC or CD)
- Peripheral arthritis, erythema nodosum & anemia **correlate** with disease activity
- Sclerosing cholangitis, ankylosing spondylitis & sacroiliitis do not correlate with disease activity
- Arthritis in IBD occurs in 3 patterns
  - a. Migratory peripheral arthritis: Non-erosive involving primarily large joints
  - b. Ankylosing spondylitis: most commonly in patients with UC & HLA-B27
  - c. Sacroiliitis: Usually asymptomatic

## Chronic Inflammatory-Like Intestinal Disorders

### A) Infections

1. Bacterial: 5 + Clostridium difficile + TB
2. Parasites: 2
3. AIDS-associated enteropathy: CMV, Cryptosporidium

### B) AIDS-associated

### C) Immunodeficiency

### D) Immune diseases

1. Behcet disease
2. Eosinophilic GE
3. GVHD

### E) Vascular disorders

1. HUS
2. HSP
3. Vasculitis: SLE...

### F) Others

1. NEC
2. Radiation colitis
3. Hirschsprung colitis
4. Diversion colitis
5. Laxative abuse

# Esophagus

## Anatomy & Function

- The esophagus can be divided into 3 areas: UES, esophageal body & LES
- **Sphincters of the esophagus**
  - Upper esophageal sphincter (UES) at the cricopharyngeus muscle
  - Lower esophageal sphincter (LES) at the GE junction
- Lower esophageal sphincter (LES) has a high resting tone "Composed of smooth muscle"
- The LES pressure ↑↑ during gastric contractions & straining
- The intra-abdominal location of the distal esophagus & LES is an important anti-reflux mechanism, because any ↑↑ in intra-abdominal pressure is also transmitted to the sphincter
- The muscularis of the upper 1/3 of the esophagus is **striated** (Cricopharyngeal dysfunction, CP)
- The muscularis of the lower 2/3 is **smooth muscle** (Achalasia)

## Diagnostic Aids

1. Barium study (with fluoroscopy): Structure & motility
2. Endoscopy (& histology)
3. Radionuclide scintigraphy scans: Evaluation of peristalsis
4. pH monitoring (± linked to polysomnography)
5. Multichannel intraluminal impedance (MII): Detect intraluminal bolus movement

# Hiatal Hernia

## Definition

- Herniation of the stomach through the esophageal hiatus (hole in the Rt crus of the diaphragm)

## Classification

- a. Sliding hernia (95%): Gastro-esophageal junction slides upwards "*Above the diaphragm*"
- b. Para-esophageal : Part of the stomach herniates without movement of G-E junction
- c. Mixed type

## Clinical Picture

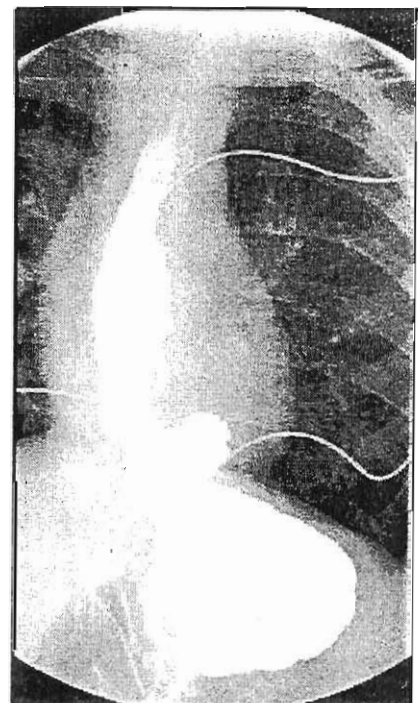
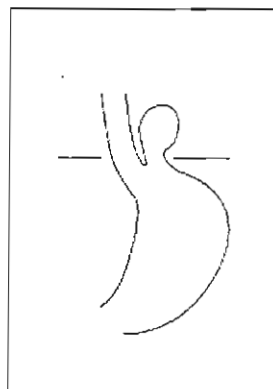
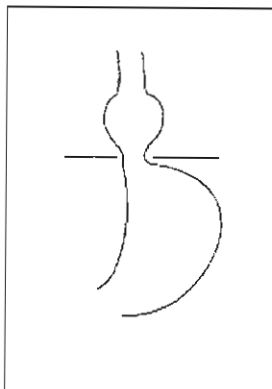
- GERD
- Para-esophageal type: Abdominal pain & fullness after meals

## Investigations

- Barium studies
- Endoscopy

## Treatment

- Medical Rx of GERD
- Surgical (Nissen fundoplication)



# Foreign Bodies in the Esophagus

## Important Remarks

- 95% of FB in the stomach pass in the GIT without difficulty
- Areas of difficulty: UES, aortic arch & LES
- Age: 6 m- 6yrs
- Coins are the commonest
- 90% of FB are radio-opaque
- C/P: Chocking, cough followed by dysphagia & vomiting (Respiratory)
  - Chocking, cough followed by dysphagia & vomiting
  - Respiratory symptoms: Stridor, wheezes & dyspnea may be present, when?
- Plain X-ray: Coin flat surface is seen in the AP view & edge in the lateral view (Trachea??)
- As a rule: Sharp objects, disk batteries & FB with respiratory symptoms should be removed
- As a rule: Blunt objects can be observed for 24 hrs

## Caustic Ingestion

### Definition

- Caustic is a substance that causes corrosion
- Alkalis: NaOH (caustic soda; paper & soap industry, cleaning agent), KOH (caustic potash)
- Acids:  $H_2SO_4$  (Sulphuric acid; used as drain cleaner & in batteries), HCl

### Properties & Action

- Alkalis: Tasteless & produce liquefaction necrosis (allowing more damage)
- Acids: Bitter & produce coagulation necrosis (protective thick eschar)

### Clinical Picture

- Severe burning pain, drooling, vomiting, dysphagia
- Respiratory: Dyspnea, stridor, cyanosis
- Oral lesions may be absent
- Shock: if perforation occurs
- Oral lesions may be absent

#### **Contraindications in corrosives**

- Emesis
- Stomach wash
- Neutralization
- Activated charcoal

### Management

#### **A. Initial management**

- Removal of the substance from the skin & eye (water flushing)
- Dilution with water, milk or egg white
- Antibiotics: to prevent 2ry infection (controversial)
- Endoscopy within 12-24 hrs

#### **B. Subsequent management**

- Endoscopic dilatation after 2 weeks
- Steroid therapy (controversial)
- Surgical repair: colon by-pass

Grade	Endoscopic Appearance
Grade 0	Normal mucosa
Grade 1	Erythema
Grade 2	Sloughing & ulceration (not circumferential)
Grade 3	Circumferential ulceration
Grade 4	Eschar, full thickness injury & perforation

# Dysphagia

## Swallowing (Deglutition)

- Swallowing is passage of "food" from the mouth through the pharynx into the esophagus
- It has 3 phases: Oral, pharyngeal & esophageal

## Definition

- Difficult swallowing (due to lesion in the oral cavity, pharynx or esophagus)
- It may be painless or painful (**Odynophagia**)
- Structural (Mechanical) defect: Solid > Fluids
- Motility (functional) defect: Fluids > Solids

## Classification & Etiology

### **A. Oropharyngeal Dysphagia**

1. Neuromuscular disorders (Dysmotility)
  - Cerebral palsy & Chiari malformation
  - Stroke
  - Multiple sclerosis
  - Cricopharyngeal achalasia: Failure of relaxation of UES
  - Cricopharyngeal incoordination: Incoordination of contraction
  - Myasthenia gravis
  - Muscular dystrophies
  - Polio, SMA
2. Collagen-vascular (Immune): SLE, sarcoidosis, dermatomyositis, amyloidosis
3. Infections: Botulism, diphtheria, Lyme disease, meningitis
4. Structural (Mechanical)
  - Stomatitis, glossitis, dental problems
  - Pharyngitis, quinsy
  - Congenital web
  - Zenker diverticulum
  - Compression: Thyroid, LN
  - Cricopharyngeal bar
  - Plummer-Vinson syndrome
  - Corrosive stricture
5. Iatrogenic: Sedatives, hypnotics, antihistamines, after tracheostomy

### **B. Esophageal Dysphagia**

- A. Neuromuscular disorders (Dysmotility)**
  - Achalasia of the cardia
  - GERD
  - Diffuse esophageal spasm: Uncoordinated esophageal contractions
  - Nutcracker esophagus: Abnormalities in neurotransmitters in the distal esophagus
- B. Mechanical**
  - a. Intrinsic**
    - FB
    - Esophagitis: GERD, eosinophilic...
    - Stricture: Peptic, corrosive
    - Diverticula
    - Esophageal web
    - Esophageal rings (Schatzki ring)
    - Tumors
    - TEF
  - b. Extrinsic**
    - Vascular ring
    - Vertebral anomalies
    - Esophageal duplication cyst
    - Mediastinal mass (LN, tumors)

#### **Zenker's diverticulum:**

Diverticulum of the pharyngeal mucosa just above the cricopharyngeal muscle (UES)  
Diagnosis: Barium swallow

# Esophageal Dysmotility

## Etiology

Upper Esophageal Dysmotility	Lower Esophageal Dysmotility
Cricopharyngeal achalasia	Achalasia of the cardia
Cricopharyngeal incoordination	GERD
Cerebral palsy & Chiari malformation	Diffuse esophageal spasm
Stroke, Multiple sclerosis	Nutcracker esophagus
Myasthenia gravis, Muscular dystrophies	
Polio, SMA	

## Achalasia

### Definition

- Esophageal motility disorder characterized by failure of relaxation of the LES & loss of esophageal peristalsis
- It may be caused by: degenerative, immune or infectious etiology
- **Allgrove syndrome:** Alacrima, achalasia, ACTH unresponsiveness

### Pathology

- Loss of inhibitory neurons (that normally lead to relaxation of the LES)

### Clinical Picture

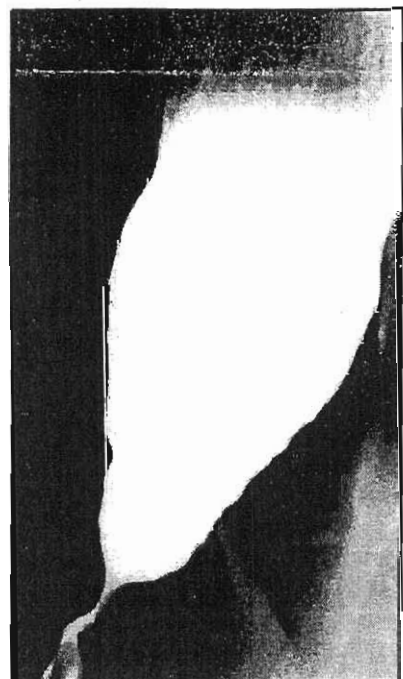
- Dysphagia (More to.....), regurgitation
- Halitosis
- Recurrent chest infection

### Investigations

- Plain X-ray: Air-fluid level
- Barium swallow: Lower end of the esophagus (Funnel-shaped, parrot-beak)
- Manometry: Most sensitive
- Endoscopy

### Treatment

- Pneumatic dilatation
- Surgical myotomy (& anti-reflux)
- Calcium channel blockers (Nifedipine): Temporary effect
- Endoscopic injection of botulinum toxin



# Gastroesophageal Reflux Disease

## (GERD)

### Definition

- Retrograde non-forcible passage of gastric contents into the esophagus
- In infants, occasional reflux is **physiologic** (Not persistent & Not frequent): 50%
- Usually mild, severe reflux is uncommon

### Epidemiology & Natural History

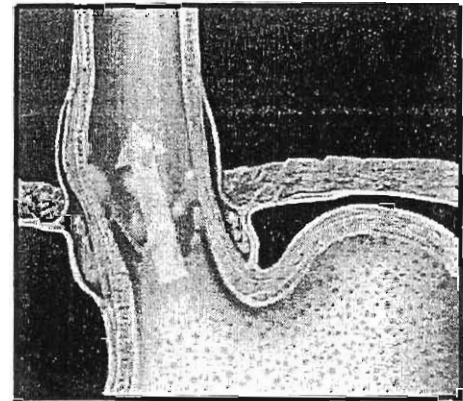
- **Infant reflux**: resolves spontaneously by the 12 months of age ( $\approx 90\%$ )
- **Reflux in older children**: Tends to be chronic (resolve in  $< 50\%$ )

### Physiology (LES)

- Lower esophageal sphincter (LES) has a high resting tone "Composed of smooth muscle"
- Intra-abdominal esophagus also acts as a physiological valve

### Etiology & Pathophysiology

- $\downarrow\downarrow$  LES tone
- $\uparrow\uparrow$  Transient LES relaxations (TLESR)
- $\uparrow\uparrow$  Intra-abdominal pressure (Straining & RD)
- Hiatal hernia
- Short intra-abdominal length of the esophagus
- Gastric distension, obesity
- Genetic predisposition



### Clinical Picture

#### A) GIT manifestations

- Excessive regurgitation
- Vomiting
- FTT & weight loss
- Esophagitis: Irritability, feeding aversion, hematemesis
- Pain

#### B) Respiratory manifestations

- Recurrent aspiration
- Chronic cough & wheezes
- Apnea, stridor, laryngitis, ALTE
- Associations: Asthma, OM, sinusitis, vocal cord nodules, hoarseness

#### C) Other manifestations

- **Sandifer syndrome**: Attacks (30 min after meals) of stiffening and opisthotonus  $\pm$  apnea & staring

### Investigations (Not routine; only in difficult or complicated patients)

- History (Questionnaires) & examination
- Extended **esophageal pH** monitoring: Best diagnostic test "% time with pH  $< 4$ "
- Barium study (Swallow & meal): *Poor sensitivity & specificity*
- Upper GI endoscopy: may show esophagitis, stricture...
- Multichannel intraluminal impedance (MII): detect intraluminal bolus movement
- Laryngotracheobronchoscopy: Inflammation, nodules, aspiration
- Empirical anti-reflux therapy: PPI...



## Complications

- Esophagitis, leading to:
  - Stricture (Distal esophagus)
  - Barrett esophagus: Mataplastic transformation of squamous epithelium into columnar epithelium (may lead to esophageal adenocarcinoma)
- Nutritional: FTT
- Respiratory: See before, why?
  - Direct contact of gastric content with the respiratory tract
  - Reflex interaction
- Apnea & stridor

## Treatment

- Reassurance
- Positioning: 30° head-up prone position after meals (with supervision, why?)
- Feeding practice: Avoid too frequent & large volume feeds
- Avoid reflux-inducing foods: juices, carbonated drinks, alcohol, chocolate, tomatoes
- Thickening of feeds (with cereals)
- Dugs:
  - Antacids (Mg & Al containing)
  - H<sub>2</sub> blockers (Cimetidine, ranitidine)
  - Proton pump inhibitor (Omeprazole...): Most potent
  - Prokinetic agents: Metoclopramide, erythromycin, domperidone
- Surgical treatment (Nissen fundoplication): refractory esophagitis

# Non-GERD Esophagitis

	Eosinophilic Esophagitis	Infective Esophagitis	Pill Esophagitis
<b>Etiology</b>	<ul style="list-style-type: none"> <li>• Allergic inflammatory condition</li> <li>• Eosinophilic infiltration</li> </ul>	<ul style="list-style-type: none"> <li>• Fungal: Candida</li> <li>• Viral: HSV, CMV, HIV, VZ</li> <li>• Bacterial: Diphtheria, TB</li> </ul>	<ul style="list-style-type: none"> <li>• Contact with irritating agent</li> <li>• NSAIDs</li> <li>• KCl</li> <li>• Ferrous sulfate</li> <li>• Tetracycline</li> </ul>
<b>Risk Factors</b>	<ul style="list-style-type: none"> <li>• Age: 1-17 (Mean = 7 yrs)</li> <li>• Atopic diseases &amp; food allergy</li> </ul>	<ul style="list-style-type: none"> <li>• Immunodeficiency</li> <li>• Immunosuppressives</li> </ul>	<ul style="list-style-type: none"> <li>• Tablet ingestion at bedtime</li> <li>• Inadequate water</li> </ul>
<b>C/P</b>	<ul style="list-style-type: none"> <li>• Vomiting</li> <li>• Dysphagia (Odynophagia)</li> <li>• Retrosternal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Dysphagia (Odynophagia)</li> <li>• Retrosternal pain</li> <li>• Fever, nausea, vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Dysphagia (Odynophagia)</li> <li>• Retrosternal pain</li> </ul>
<b>Complications</b>	<ul style="list-style-type: none"> <li>• Stricture</li> </ul>	<ul style="list-style-type: none"> <li>• Stricture</li> </ul>	<ul style="list-style-type: none"> <li>• Stricture</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>• CBC: Eosinophilia</li> <li>• IgE: ↑↑</li> <li>• Skin prick &amp; patch tests</li> <li>• Barium swallow: Ringed esophagus</li> <li>• Endoscopy: granular, rings, furrows, exudates</li> <li>• Biopsy: Heavy infiltration with eosinophils (&gt; 15-20/HPF)</li> </ul>	<ul style="list-style-type: none"> <li>• Endoscopy: ulcers, exudates</li> <li>• Biopsy</li> <li>• PCR, viral culture</li> </ul>	<ul style="list-style-type: none"> <li>• Endoscopy: Focal lesion (?site)</li> <li>• Biopsy</li> <li>• PCR, viral culture</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Dietary restriction: <ul style="list-style-type: none"> <li>➢ Elimination</li> <li>➢ Six food elimination diet (milk, egg, wheat, soy, seafood, peanut, tree nuts)</li> <li>➢ Elemental diet (amino acid-based)</li> </ul> </li> <li>• Topical &amp; systemic steroids</li> <li>• Anti-IL-5 antibody (Mepolizumab)</li> </ul>	<ul style="list-style-type: none"> <li>• Antimicrobial agents</li> <li>• Analgesics</li> <li>• Antacids</li> </ul>	<ul style="list-style-type: none"> <li>• Analgesics</li> <li>• Antacids</li> <li>• Liquid diet</li> </ul>

# Acute Abdominal Pain

## Importance

- It is a common pediatric medical emergency
- In young children diagnosis of acute appendicitis should not be delayed [progression to perforation can be rapid]
- Of the surgical causes, acute appendicitis is the most common

## Etiology

### A) Medical Causes

#### a. Acute abdominal infections

- Most common cause of acute abdominal pain
- Differentiation depends on the site of pain & associated manifestations

	Site of pain	Associated manifestations
Gastroenteritis	Epigastric	Diarrhea, vomiting
Hepatitis	Rt Hypochondrial	Jaundice, dark urine
Appendicitis	Periumbilical then RLQ	Rebound tenderness, cough tenderness
Cholecystitis	Rt hypochondrial	Hemolytic anemia, jaundice
Pyelonephritis	Loin (Rt or Lt)	Fever, rigors, dysuria
Peritonitis	Diffuse	Vomiting, distension, rigidity, guarding
Pancreatitis	Epigastric	Pain radiating to the back
URI	Mesenteric adenitis	Follicular tonsillitis

#### b. Acute medical conditions

1. Henoch-Schonlein purpura
2. Lower lobe pneumonia (Right side)
3. DKA
4. Drug intoxication: NSAIDs
5. Sick cell anemia (Rt upper quadrant syndrome; Vaso-occlusive crisis)
6. Stones
7. Acute rheumatic fever
8. Acute porphyria
9. Lead poisoning
10. FMF

### B) Surgical Causes

- a. Acute appendicitis
- b. Inflamed Meckel diverticulum
- c. Ureteric obstruction
- d. Testicular torsion
- e. Ruptured ectopic pregnancy
- f. Strangulated inguinal hernia
- g. Intussusception
- h. Malrotation, Volvulus
- i. Impacted fecal masses
- j. Worm masses

= Causes of  
intestinal obstruction



## Investigations (Depend on the suspected etiology)

- ☑ **Laboratory:** CBC, CRP, ESR, Urinalysis, liver enzymes...
- ☑ **Imaging:** X-rays abdomen, Abdominal US

## Treatment Rx of the cause

# Chronic Abdominal Pain

## Definitions

Term	Definition
Chronic abdominal pain	Long-standing intermittent or constant abdominal pain (May be functional or organic)
Functional abdominal pain	Chronic abdominal pain with No evidence of pathologic condition (Anatomic, metabolic, infectious, inflammatory or neoplastic)
Functional dyspepsia	Functional abdominal pain (in the upper abdomen)
Irritable bowel syndrome	Functional abdominal pain or discomfort with 2 of the following: <ul style="list-style-type: none"> <li>➤ Improved with defecation</li> <li>➤ Change in stool frequency (Increased or decreased)</li> <li>➤ Change in stool consistency (Hard or loose)</li> </ul>
Abdominal migraine	Functional abdominal pain (with nausea, vomiting, anorexia or pallor)

## Incidence

- Chronic abdominal pain: Common [10-15% of all children (♀ > ♂)]

## Pathophysiology

- Not clear; visceral hypersensitivity, motility disturbances, inflammatory (Mediators), abnormalities of the enteric nervous system, altered intestinal permeability, psychological

## Evaluation

A. Thorough history & examination

B. Alarm symptoms & signs (Need for further investigations)

Symptoms	Signs
Persistent RUQ or RLQ	Localized tenderness in the RUQ or RLQ
Pain that wakes up the child from sleep	Localized fullness or mass
Weight loss	Loin tenderness
GI blood loss	Perianal disease
Dysphagia	HSM
Significant vomiting (bilious, protracted, cyclic)	Jaundice
Chronic diarrhea or nocturnal diarrhea	Arthritis
GU symptoms	Spinal tenderness
Unexplained fever	Abnormal or unexplained physical findings
Delayed puberty	
Affection of growth	
Family history of IBD, celiac disease or PUD	

C. Simple investigations (CBC, CRP, ESR, urinalysis, stool analysis & culture, celiac)

D. Other investigations: Tests for H. pylori, H<sub>2</sub> breath test, why?, abdominal US

E. Other investigations

## Classification & Etiology of Chronic Abdominal Pain

		Functional abdominal pain (Psychogenic, Nonorganic)	Organic abdominal pain
Incidence		> 90%	< 10%
Pain	☒ Site	Periumbilical (central) location is characteristic	➤ Away from the umbilicus ➤ Likelihood of being organic is directly <u>proportionate</u> to the distance from the umbilicus <ul style="list-style-type: none"> <li>▪ Renal colic (Loin)</li> <li>▪ Peptic ulcer (Epigastric)</li> <li>▪ Chronic constipation (Lt iliac)</li> <li>▪ Chronic hepatitis (RUQ)</li> </ul>
	☒ Nature	Vague (Dull aching)	Variable (Stitching...)
	☒ Severity	Not severe	May be severe (waking child at night)
	☒ Duration	Subside in < 20 min	Variable
Appearance		Healthy	May be toxic
Association		No	Alarm symptoms & signs
Abdominal Examination		Normal	Focal tenderness Organomegaly or masses
Simple investigations?		Normal (CBC, ESR, CRP, UA, stool)	Commonly abnormal
Treatment		Reassurance Education	Rx of the cause
Etiology & Predisposing factors		Unknown?? <ul style="list-style-type: none"> <li>➤ Social               <ul style="list-style-type: none"> <li>- Family problems</li> <li>- Loss of parent</li> <li>- Delivery of new sibling</li> </ul> </li> <li>➤ School phobia</li> <li>➤ To gain love &amp; sympathy</li> <li>➤ Imitation of adults</li> </ul>	<ul style="list-style-type: none"> <li>○ Parasitic infestations</li> <li>○ Chronic constipation</li> <li>○ Dietetic: bad selection</li> <li>○ Drugs: NSAIDs</li> <li>○ Lactose intolerance</li> <li>○ UTI, renal stones</li> <li>○ Esophagitis, gastritis, PUD</li> <li>○ IBD</li> <li>○ Sickle cell anemia</li> <li>○ GB stones</li> <li>○ Chronic hepatitis</li> <li>○ FMF</li> <li>○ Lead poisoning</li> <li>○ Dysmenorrhea, ovarian cysts</li> </ul>

### Treatment (Functional abdominal pain)

- Explain that pain is **real** but there is no underlying serious disease; some may resist
- Disappearance of pain is not a reasonable goal
- Parents should avoid "2ry gain"
- Children should return to regular activities & school
- Behavioral therapy, biofeedback, relaxation techniques
- Drugs: Acid suppressants, antispasmodics, LD amitriptyline
- Peppermint oil
- Diet: Lactose-restricted diet, fiber supplementation

# Oral Ulcers

	Comment
<b>Aphthous ulcer (Canker sores)</b>	<ul style="list-style-type: none"> <li>• Unknown etiology(?allergic, immune, genetic)</li> <li>• Recurrence is common</li> <li>• Affecting 20% of population</li> <li>• Associations: IBD, Behçet, celiac, PFAPA, HIV, cyclic neutropenia</li> <li>• Well-circumscribed ulcers surrounded by erythematous ring</li> <li>• Duration: 10-14 days</li> <li>• TTT: Symptomatic, topical lidocaine, tetracycline?</li> </ul>
<b>Traumatic ulcer</b>	<ul style="list-style-type: none"> <li>• Accidents</li> <li>• Cheek biter</li> </ul>
<b>Herpetic Gingivostomatitis</b>	
<b>Herpangina</b>	
<b>Recurrent herpes labialis</b>	<ul style="list-style-type: none"> <li>• Reactivation of HSV</li> <li>• Recurrence is common (Stress, UVR, trauma)</li> <li>• Limited to the lips (vesicles &amp; ulcers)</li> <li>• Painful &amp; disfiguring</li> <li>• No systemic manifestations</li> <li>• TTT: Symptomatic (No need for acyclovir)</li> </ul>
<b>Hand, foot, mouth disease</b>	<ul style="list-style-type: none"> <li>• Etiology: Coxsackievirus A &amp; B, enterovirus 71, echoviruses</li> <li>• C/P: Pharyngeal inflammation, vesicles on the tongue &amp; oral mucosa Vesiculo-pustular rash on the hands, feet &amp; buttocks</li> <li>• Duration: 7 days</li> <li>• Complications: Brainstem encephalomyelitis, myocarditis, shock</li> </ul>
<b>Acute necrotizing ulcerative gingivitis (Vincent's angina)</b>	<ul style="list-style-type: none"> <li>• Etiology: Oral spirochetes and fusobacteria</li> <li>• C/P: Necrosis, ulceration &amp; bleeding of gingiva Formation of adherent grayish pseudomembrane Halitosis Fever, malaise, cervical LN</li> <li>• It can extend to adjacent tissue causing necrosis of facial structures (cancrum oris or noma)</li> <li>• DD: Herpetic gingivostomatitis</li> <li>• Dark-field microscopy: Spirochete</li> <li>• TTT: local debridement, oxygenating agents, analgesics, antibiotics (penicillin or metronidazole)</li> </ul>
<b>Chemical burn</b>	<ul style="list-style-type: none"> <li>• Acids, alkalis</li> </ul>
<b>Heat burn</b>	<ul style="list-style-type: none"> <li>• Hot food</li> </ul>
<b>Neutrophil defect</b>	<ul style="list-style-type: none"> <li>• Cyclic neutropenia, leukemia, aplastic anemia</li> </ul>
<b>SLE</b>	<ul style="list-style-type: none"> <li>• Recurrent, may be painless</li> </ul>
<b>Behcet</b>	<ul style="list-style-type: none"> <li>• Genital ulcers &amp; uveitis</li> </ul>
<b>Crohn</b>	<ul style="list-style-type: none"> <li>• Painful</li> </ul>
<b>Syphilis</b>	<ul style="list-style-type: none"> <li>• Painless chancre</li> </ul>
<b>Histoplasmosis</b>	<ul style="list-style-type: none"> <li>• Lingual</li> </ul>

# Vomiting

## Definition

Forceful expulsion of gastric contents through the mouth

## Etiology

### A) Neonatal Vomiting

#### a. Healthy neonates

##### ☒ Milk

- Gastroesophageal reflux disease (GERD)
- Over/Irregular feeding

##### ☒ Mucoid

- Amniotic gastritis

##### ☒ Blood, source may be:

- Neonatal: Hemorrhagic disease of the newborn (Vitamin K deficiency)
- Maternal: Swallowed maternal blood (Birth canal)

#### b. Sick neonates

##### ☒ Medical causes

- Infection: Septicemia, gastroenteritis, UTI
- Inborn errors of metabolism: Galactosemia, tyrosinemia, urea cycle defects
- ↑↑ ICP: ICH, CNS infections

##### ☒ Surgical causes

- Non-bile stained: Tracheoesophageal fistula (*1<sup>st</sup> feed*) & CHPS
- Bile-stained: Congenital intestinal obstruction (e.g., Intestinal atresia...)

### B) Vomiting in Infancy & Childhood

#### c. Medical:

##### ☒ Dietetic & GIT disorders:

- Overfeeding, irregular feeding or inappropriate foods
- Drugs
- GERD
- Food poisoning
- Gastritis, esophagitis, peptic ulcer, pancreatitis, biliary colic, IBD

##### ☒ Infection:

- Respiratory infection: Pneumonia, bronchitis, pertussis, OM, sinusitis
- GIT infections: GE, hepatitis, appendicitis, cholecystitis
- Other systemic infections: UTI (pyelonephritis), obstructive uropathy

##### ☒ Metabolic

- Diabetic ketoacidosis (DKA)
- Renal: CRF, RTA, Bartter syndrome, renal colic, renal stone
- Congenital adrenal hyperplasia
- Hypervitaminosis D
- Inborn errors of metabolism
- Reye syndrome
- Chemotherapy

##### ☒ Central (↑↑ ICP): CNS infection, ICH, concussion, brain tumors

##### ☒ Others: Migraine, cyclic vomiting, familial dysautonomia, factitious syndrome

#### d. Surgical: Intestinal obstruction (*Causes*)

### Complications of Vomiting

- Metabolic: Dehydration, alkalosis, ↓↓ Cl, ↓↓ K, ↓↓ Na
- Nutritional: FTT
- Mallory-Weiss: Hematemesis
- Esophagitis
- Aspiration
- Shock
- Pneumothorax, pneumomediastinum
- Retinal hemorrhage

### Cyclic Vomiting

**Definition:** One of the FGIDs characterized by attacks of vomiting with free intervals

**Mechanism:** Unknown? Autonomic dysfunction, mitochondrial, migraine-related

**Usual frequency:** 12/year, each lasts for 2-3 days with 4 emesis episodes /hour

**Triggering factors:** Physical stress, psychological stress, infection

**Diagnostic Criteria:**

- ☑ ≥ 2 episodes of intense nausea & vomiting lasting hours to days
- ☑ Return to usual status in between for weeks or months

**Prevention:** Amitriptyline, Propranolol, Cyproheptadine

**Treatment:** Hydration, Anti-emetics

Condition	T.T
GERD & Gastroparesis	▪ Dopamine antagonist (Metoclopramide)
Intestinal pseudo-obstruction	▪ Octreotide
Chemotherapy	<ul style="list-style-type: none"> <li>▪ Dopamine antagonist (Metoclopramide)</li> <li>▪ Serotonergic antagonist (Ondansetron)</li> <li>▪ Phenothiazines (Chlorpromazine)</li> <li>▪ Steroids (Dexamethasone)</li> </ul>
Postoperative	<ul style="list-style-type: none"> <li>▪ Serotonergic antagonist (Ondansetron)</li> <li>▪ Phenothiazines (Chlorpromazine)</li> </ul>
Motion sickness & vestibular disorders	<ul style="list-style-type: none"> <li>▪ Antihistamine (Dimenhydrinate)</li> <li>▪ Anticholinergic (Scopolamine, hyoscine)</li> </ul>
Adrenal crisis	▪ Steroids (Cortisol)
Cyclic vomiting syndrome	<ul style="list-style-type: none"> <li>▪ Supportive <ul style="list-style-type: none"> <li>➢ Antihistamine: Diphenhydramine</li> </ul> </li> <li>▪ Abortive <ul style="list-style-type: none"> <li>➢ Serotonergic antagonist (Ondansetron)</li> <li>➢ Serotonergic agonist (Sumatriptan)</li> </ul> </li> <li>▪ Prophylactic <ul style="list-style-type: none"> <li>➢ Amitriptyline (Antidepressant)</li> <li>➢ Propranolol (β-blocker)</li> </ul> </li> </ul>



# Acute Pancreatitis

## Definition

- Acute inflammation of the pancreas (*It leaves the pancreas completely free*)

## Etiology

<b>Drugs &amp; Toxins</b>	<ul style="list-style-type: none"> <li>• Acetaminophen, alcohol, azathioprine</li> <li>• Asparaginase, vincristine, 6-mercaptopurine</li> <li>• Corticosteroids, cimetidine</li> <li>• Erythromycin, estrogen</li> <li>• Furosemide, thiazides</li> <li>• Sulfonamide (mesalamine 5-ASA, SMZ-TMP), tetracycline</li> <li>• Venom, valproic acid</li> </ul>
<b>Genetic</b>	<ul style="list-style-type: none"> <li>• Cystic fibrosis</li> <li>• Trypsinogen gene, chymotrypsin gene, trypsin inhibitor</li> </ul>
<b>Infections</b>	<ul style="list-style-type: none"> <li>• MMR, HAV, HBV, Influenza A&amp;B, VZ, EBV, coxsackie B</li> <li>• Ascaris, malaria</li> <li>• Septic shock</li> </ul>
<b>Obstruction</b>	<ul style="list-style-type: none"> <li>• Ampullary disease, ascaris</li> <li>• Bile tract malformation, choledochal cyst, cholelithiasis</li> <li>• Pancreatic duct malformation</li> <li>• Pancreatic divisum: 2 separate pancreatic ducts</li> <li>• ERCP complication</li> <li>• Tumors, trauma (operative)</li> </ul>
<b>Systemic</b>	<ul style="list-style-type: none"> <li>• Collagen-vascular diseases</li> <li>• SLE, Kawasaki, vasculitis, PAN</li> <li>• Hyperlipidemia, Hypercalcemia, hyperparathyroidism</li> <li>• Crohn, peptic ulcer</li> <li>• Malnutrition, DM, Hemochromatosis</li> <li>• HUS, Renal failure</li> </ul>
<b>Trauma</b>	<ul style="list-style-type: none"> <li>• Blunt trauma, child abuse, surgery, hypothermia</li> </ul>

## Pathophysiology

- Normally, proteolytic enzymes of the pancreas are secreted in an inactive form
- Activated in the lumen of the duodenum
- Premature activation leads to pancreatitis (autodigestion)
- Edema, hemorrhage, necrosis of the pancreas
- Peripancreatic tissue: Fat necrosis (saponification of fat) & hemorrhage
- Systemic effects: ↑↑ amylase & lipase, ↓↓ Ca, VD, MOSF, ARDS, DIC
- Complications: pancreatic abscess, pancreatic pseudocyst

## DD of ↑↑ amylase

Pancreatic pathology	Salivary gland pathology	Intra-abdominal pathology
<ul style="list-style-type: none"> <li>▪ Acute pancreatitis</li> <li>▪ Chronic pancreatitis</li> <li>▪ Complicated pancreatitis</li> <li>▪ GVHD</li> </ul>	<ul style="list-style-type: none"> <li>▪ Parotitis (Mumps, CMV)</li> <li>▪ Sialadenitis (Calculus)</li> <li>▪ Anorexia nervosa</li> <li>▪ Bulimia</li> </ul>	<ul style="list-style-type: none"> <li>▪ GB stones</li> <li>▪ Peptic ulcer perforation</li> <li>▪ Peritonitis, Appendicitis</li> <li>▪ Intestinal obstruction</li> </ul>
<b>Systemic diseases</b>	Metabolic acidosis (shock, DM), pregnancy, cardiopulmonary bypass, burns, head injury, renal failure	

## Clinical Picture

### a. Mild cases:

- Acute abdominal pain (Epigastric radiating to the back)
- Anorexia, nausea, vomiting
- Abdominal tenderness
- Good prognosis

### b. Severe cases:

- Shock, high fever, jaundice, ascites, tetany
- Discoloration of the flanks (**Grey-Turner sign**)
- Discoloration around the umbilicus (**Cullen sign**)
- Systemic effects
- Mortality is 20%

## Investigations

- Serum lipase (↑↑ at 4 hrs; peaks at 24-48 hrs & remains for 8-14 days)
- Serum amylase
- Leukocytosis, DIC, hyperglycemia, glucosuria, hypocalcemia, ↑↑ Bilirubin
- Abdominal X-ray: Sentinel loop, colon cut-off sign, calcification, GB stones
- Abdominal US & CT: pancreatic edema (enlargement), abscess, fluid collection
- MRCP, ERCP

## Treatment

- Hospitalization
- NPO, NGT, IVF
- Maintenance of fluid & electrolyte balance
- Early refeeding (After control of vomiting)
- Prophylactic antibiotics
- Endoscopic management: Stricture or stones
- Surgical management: Rarely indicated (Drainage of necrotic material or abscess)

## Prognosis

- Uncomplicated acute pancreatitis: Good with recovery within 4-5 days
- Cases associated with systemic disease: prognosis is related to the associated condition

# Intussusception

## Incidence

- Most common cause of intestinal obstruction in infancy
- Age: 3 months- 3 yrs (Peak = 6 months)

## Etiology

- Unknown, it usually follows an attack of GE
- Hypertrophy of Payer's patches

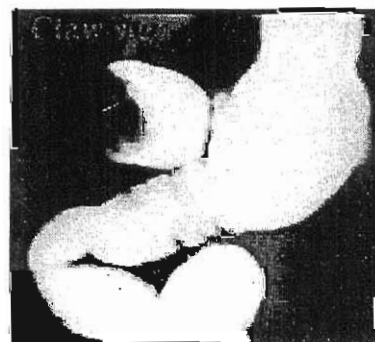
## Clinical Picture

- Abdominal **pain**: Sudden, severe, paroxysmal, colicky abdominal pain with pallor
- The pain **recurs** at frequent intervals
- Initially the infant looks well **in between**
- Vomiting may be frequent early
- **Red currant jelly stools**: Mucus & blood in stools
- **Abdominal mass**: sausage-shaped in the Rt upper quadrant (70 %)
- **PR examination**: Mucus & blood on the examining finger
- If **neglected**: Shock-like state, bilious vomiting & abdominal distension (Gangrene)

→ Abdominal  
 → Rectal  
 → Bimanual

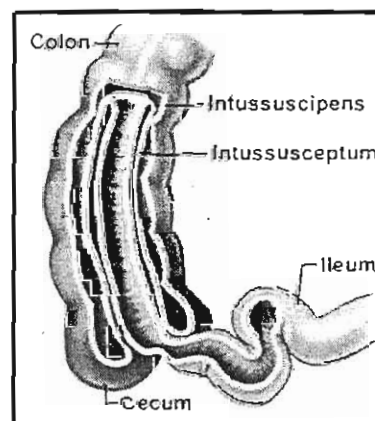
## Investigations

- ☑ Abdominal US
- ☑ Plain X-rays abdomen: Air-fluid levels
- ☑ Barium enema: Claw sign or coiled-spring sign ⇒



## Treatment (Depends on the time of presentation)

- ☑ Air enema: Pneumatic reduction
- ☑ Resection-anastomosis: In neglected cases



# Gastrointestinal Bleeding

## Hematemesis

### Definition

- Vomiting of blood due to lesion in the upper GIT (esophagus, stomach & duodenum)
- It may be altered "coffee ground" (Mild to moderate bleeding) or red (Massive bleeding)

### Common Causes

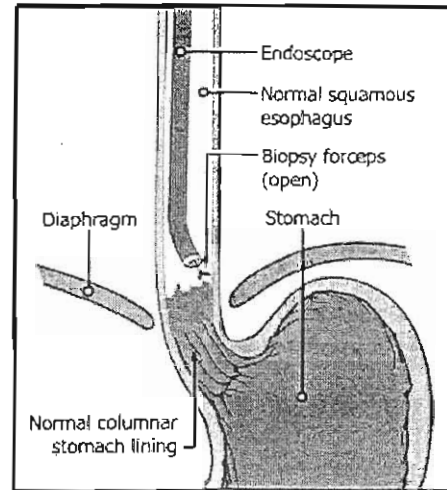
1. Swallowed blood
2. Esophagitis
3. Esophageal varices
4. Gastritis
5. Peptic ulcer
6. Foreign body
7. General causes of bleeding (ITP, hemophilia...)

### Investigations

- Upper GI endoscopy is essential for diagnosis

### Treatment

- Rx of the cause e.g., Sclerotherapy for varices...



## Bleeding Per Rectum

### Definition

It is passage of blood per rectum. It may be:

- Fresh bright red blood (**Hematochezia**): It indicates either distal bleeding site or massive upper GI bleeding above the distal ileum
- Black tarry stools (**Melena**): It indicates a bleeding site above the distal ileum

### Common Causes

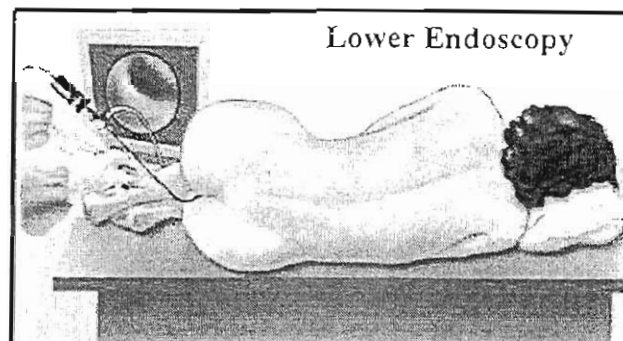
1. All causes of hematemesis
2. Anal fissure
3. Polyps
4. Bloody diarrhea
5. Inflammatory bowel disease (Ulcerative colitis)
6. Intussusception
7. Henoch-Scholein purpura
8. Necrotizing enterocolitis
9. Hemorrhagic disease of the newborn
10. Meckel's diverticulum

### Investigations

- Stool analysis
- Barium enema
- Lower GI endoscopy

### Treatment

- Rx of the cause e.g., Removal of polyps...



**PEDIATRIC  
HEPATOLOGY**

**BY  
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**2009**

# Hepatology

## Liver Functions

1. **Protein metabolism** (Synthesis of albumin, globulins, coagulation factors, urea cycle)
2. **Carbohydrate metabolism** (Glycogenesis, glycogenolysis, gluconeogenesis)
3. **Lipid metabolism**
4. **Bile pigment metabolism**
5. **Bile salts metabolism**
6. **Endocrine function** (Vitamin D activation, EPO, catabolism of hormones)
7. **Hematopoietic function**
8. **Detoxification of drugs & toxins**

## Liver Function Tests

### A) Tests related to Proteins

#### 1. Plasma proteins

##### ☒ Albumin

- Not affected in acute liver disease
- ↓↓ in chronic liver disease

##### ☒ Globulins

- ↑↑ in chronic liver disease
- ↑↑ in immune liver diseases

**Albumin has long half-life = 16-24 days**

#### 2. Prothrombin time

- Normally = 10-13 sec
- ↑↑ in liver cell failure (acute & chronic) & in obstructive jaundice. DD??

**PT is the most sensitive liver function**

#### 3. Blood ammonia level

### B) Tests related to Bile pigments

#### 1. Serum bilirubin

##### ☒ Total bilirubin

##### ☒ Direct bilirubin

#### 2. Urine bilirubin

- Only direct bilirubin
- ↑↑ in OJ (cholestasis)

#### 3. Urine urobilinogen

- ↑↑ in hemolytic jaundice
- ↓↓ in OJ (cholestasis)

#### 4. Stools stercobilinogen

- ↑↑ in hemolytic jaundice
- ↓↓ in OJ (cholestasis)

Unconjugated bilirubin	Conjugated bilirubin
Hemobilirubin	Cholebilirubin
Indirect bilirubin	Direct bilirubin
Bound to albumin	Not bound
Water insoluble	Water soluble
Can't be excreted in urine	Can be excreted in urine

#### Cholestasis:

1. Direct bilirubin > 2 mg/dl OR
2. Direct bilirubin > 20 % of total bilirubin

### C) Tests related to Bile salts

1. Serum bile salts } ↑↑ in cholestasis
2. Urine bile salts }

### D) Liver enzymes

1. ALT, AST, ALP
2. γ-glutamyl transpeptidase (GGT)
3. 5'-nucleotidase



### E) Tests related to CHO & fat metabolism Glucose, cholesterol...

# Portal Hypertension

## Definition

Increased portal venous pressure > 12 mmHg or 15 cm H<sub>2</sub>O

↑↑ ICP > 15 mmHg or 200cm H<sub>2</sub>O  
C/P of ↑↑ ICP if > 25 mmHg

## Etiology

### A) Prehepatic Causes

1. Portal vein thrombosis
2. Splenic vein thrombosis
3. Umbilical vein catheterization
4. Umbilical sepsis
5. Neonatal sepsis
6. Portal vein agenesis, atresia or cavernous transformation
7. Hereditary tendency to thrombosis (6)
8. Trauma
9. AV fistula between hepatic artery & portal vein
10. Primary (idiopathic) portal hypertension

### B) Intrahepatic Causes

1. Presinusoidal
  - a. Portal tract fibrosis: Bilharziasis & Congenital hepatic fibrosis
  - b. Portal tract infiltration: Leukemia, lymphoma
2. Sinusoidal
  - a. Cirrhosis
  - b. Cryptogenic
3. Postsinusoidal
  - Veno-occlusive disease

### C) Posthepatic Causes

1. Budd-Chiari
2. IVC obstruction (Thrombosis or masses)
3. Congestive HF, Constrictive pericarditis, Pericardial effusion, Tricuspid valve disease

## Pathological Effects

### A) Congestion of abdominal viscera drained by portal vein

- Splenomegaly
- GIT congestion: Gastric ulcers, malabsorption

### B) Opening of porto-systemic collaterals

- Esophageal varices
- Anorectal varices
- Caput medusa
- Others: Retroperitoneal connections, visceral surfaces...

### C) Deterioration of liver function [Manifestations of liver cell failure]

- Primary liver disease: Cirrhosis
- Prehepatic causes: ↓↓ Portal blood flow to the liver
- Posthepatic causes: Hepatic congestion

### D) Ascites:

- Deterioration of liver function (↓↓ Albumin...)
- ↑↑ Salt & H<sub>2</sub>O (↑↑ ADH, ↑↑ Aldosterone)
- Portal hypertension is a localizing factor
- ↑↑ Hepatic lymph production (Lymphorrhea)
- ↑↑ Incidence of bacterial peritonitis

## Clinical Picture

- Picture of the cause
- Hepatomegaly
- Splenomegaly
- Ascites
- Bleeding esophageal varices (Hematemesis ± Melena)
- Dilated veins on the anterior abdominal wall
- Manifestations of liver cell failure

**Splenomegaly is the most important diagnostic sign of portal hypertension**

### **Causes of bleeding:**

1. Trauma by food
2. Gastritis or esophagitis (NSAIDs)
3. Straining (Cough)


**Melena:** Dark, altered blood due to bleeding above D/J junction

## Investigations

### A) Laboratory

- ☒ Liver function tests
- ☒ CBC (anemia, pancytopenia, ↑↑ Eosinophils...)

### B) Imaging

- ☒ Barium swallow?
- ☒ Abdominal US & Doppler 
- ☒ CT, MRI, MRA
- ☒ Splenoportography (Splenic vein)
- ☒ Transhepatic portography
- ☒ Selective catheterization of the celiac axis or the superior mesenteric artery

### **Value of US:**

1. Assessment of liver, spleen, ascites
2. Estimation of portal venous pressure
3. Direction of blood flow in portal vein
4. Primary etiology

### C) Invasive

- ☒ Upper endoscopy: Esophageal or gastric varices & ulcers
- ☒ Portal manometry
  - Intrasplenic pressure measurement
  - Wedged hepatic venous pressure (WHVP): to measure postsinusoidal pressure
  - Intra-operative measurement of portal venous pressure
- ☒ Liver biopsy

## Approach to a case of portal hypertension

### A) History

Admission to NICU, exchange transfusion, cardiac symptoms, LCF, bleeding

### B) Examination

Splenomegaly: Most important sign of portal hypertension

Hepatomegaly: Absent (prehepatic), shrunken (Cirrhosis), marked (Posthepatic)

Ascites: especially in cirrhosis

### C) Investigations

LFTs are usually normal in prehepatic & presinusoidal causes



## Treatment of Portal Hypertension

### A) Portal hypertension with active GIT bleeding

1. Stabilization of the patient [A, B, C]
2. Monitoring of vital signs
3. Vascular access + Fluid therapy (Shock therapy) →
4. Vitamin K
5. Transfusion
  - Blood: Use fresh blood, why? →
  - FFP
  - Platelets
6. H<sub>2</sub> blockers (Ranitidine or Cimetidine)
7. NGT: for diagnosis & monitoring if ongoing blood loss
8. Stomach wash (Not ice cold saline)
9. Prevention & Rx of hepatic encephalopathy
10. Measures to stop bleeding
  - a. Medical:
    - Vasopressin
      - Action: VC of the splanchnic BV → ↓↓ Portal blood flow
      - Dose: Bolus (0.33U/Kg over 20 minutes) followed by continuous infusion
      - Side effects: Impairment of cardiac function, ↓↓ BF to liver, intestines, kidney
      - Nitroglycerin skin patch may be used to avoid such complications
    - Glypressin: Less side effects
    - Synthetic somatostatin analog (Octreotide) = Sandostatin
      - Dose: 1-5 µg/Kg/hr
      - Less side effects
  - b. Endoscopic:
    - Injection sclerotherapy: Using Ethanolamine oleate or Histoacryl
    - Band ligation (?Less side effects)
  - c. Sengstaken tube: Mechanical compression in refractory cases
  - d. Surgical:
    - Porto-systemic shunts
      - Action: ↓↓ Portal pressure
      - Types: Total (Porto-caval) or Selective (Distal spleno-renal) or TIPS
      - Side effects: ↑↑ Risk of hepatic encephalopathy (Total > Selective)
    - Vasoligation with esophageal stapling

Avoid lactated Ringer's, why?

Avoid ↑↑ volume, why?

Avoid old blood, why?

Technically challenging

### B) Prophylactic management of portal hypertension

1. Medical: Propranolol (1-4 mg/Kg/day) guided by ↓↓ HR (25% Reduction)
2. Endoscopic: Regular injection sclerotherapy
3. Surgical: Shunt operations
4. Liver transplantation

# Liver Cirrhosis

## Definition

Chronic diffuse irreversible liver disease characterized by degeneration of liver cells & the formation of regeneration nodules with irreversible loss of liver architecture

## Etiology

1. Infection: Post-hepatitic (B, C, D)
2. Drugs & toxins: Alcohol, INH, MTX
3. Cardiac cirrhosis
4. Biliary cirrhosis
5. Metabolic
  - Wilson
  - $\alpha$ -1-Antitrypsin deficiency
  - Hemochromatosis (NID)
  - GSD type IV
  - Galactosemia, hereditary fructose intolerance
  - Tyrosinemia
6. Autoimmune hepatitis
7. Cryptogenic

## Classification

### A) Etiological

### B) Pathological

- a. Micronodular (< 1 cm)
- b. Macronodular
- c. Mixed

### C) Functional

- a. Compensated (Latent)
- b. Decompensated (Manifest)

## Clinical Picture

A) **Compensated:** Discovered accidentally (Examination or imaging)

B) **Decompensated**

1. Liver cell failure
2. Portal hypertension
3. Others: Hepatocellular carcinoma, infection...

**On Examination:** Liver is firm, shrunken\* with sharp border

## Investigations

A) **Laboratory:** Liver function tests

B) **Imaging:** Abdominal US, CT, MRI

C) **Invasive:** Liver biopsy

D) **Investigation of the cause** (Hepatitis markers...)

E) **Investigations of portal hypertension** (Upper GIT endoscopy...)

F) **Investigations of complications** (AFP level, US, CT, MRI...)

## Treatment

A) **Rx of the cause:** Avoid alcohol, Steroids for autoimmune hepatitis, Rx of cholestasis...

B) **Rx of liver cell failure**

C) **Rx of portal hypertension**

D) **Rx of complications:** Hepatic encephalopathy, Ascites, Hepatocellular carcinoma

E) **Liver transplantation**

# Liver Cell Failure

## Definition

Impairment of liver functions,

## Clinical Picture

### 1. General Failure of health

- Anorexia, easy fatigability
- Cause: Disturbed anabolic function of the liver

### 2. Fever

- Low-grade fever (Bacteremia)
- Cause: Intestinal bacteria pass through the diseased liver without elimination or bypass the liver through P/S shunts to reach the general circulation

### 3. Fetor hepaticus

- Mousy odor
- Cause: Maercaptans produced by intestinal bacteria reach the general circulation, how??

### 4. Jaundice

- Cause: ↓↓ Uptake, conjugation & excretion of bilirubin

### 5. Ascites & edema

### 6. Hepatic encephalopathy

### 7. Endocrinal

- ♂: Gynecomastia
- ♀: Amenorrhea

### 8. Cutaneous manifestations

- White nail
- Parotid enlargement
- Palmar erythema (Eythema with central palmar pallor)
- Spider nevi (Dilated arteriole with radiating capillaries in the distribution of SVC)

### 9. CVS manifestations

- Hyperdynamic circulation (↑↑ VD substances; e.g. PGs...)
- Porto-pulmonary shunts

### 10. Hematological

- Anemia: Bleeding, hypersplenism, nutritional
- Pancytopenia: Hypersplenism
- Bleeding tendency: Platelet dysfunction, Thrombocytopenia, Acquired coagulopathy

### 11. Hepatorenal

- **Definition:** Renal failure with **normal** renal histology occurring in patients with LCF

#### - Mechanism:

- ↓↓ Effective plasma volume
- VC of renal BV

Functional

#### - Precipitating factors:

- Diuretics
- Diarrhea
- Bleeding
- Paracentesis
- Sepsis

- **Prognosis:** Very poor

### 12. Infection: Spontaneous bacterial peritonitis

### 13. Metabolic: Hypoglycemia or hyperglycemia

### 14. Picture of the cause: Cirrhosis (Bleeding varices)

#### Causes of Ascites:

1. Hypoalbuminemia (↓↓ Oncotic P.)
2. ↑↑ Salt & H<sub>2</sub>O (↑↑ ADH, ↑↑ Aldosterone)
3. Portal hypertension (Localizing factor)
4. Lymphorrhea
5. ↑↑ Incidence of bacterial peritonitis

## Veno-Occlusive Disease

### Definition

Intrahepatic postsinusoidal portal HTN due to affection of the endothelial lining of hepatic veins tributaries

### Etiology (Unknown)

- ☒ Herbal tea & alkaloids
- ☒ Hepatic irradiation
- ☒ Egyptian type: Malnutrition & infection

### Pathology

- ☒ Egyptian type: Thrombosis
- ☒ Jainayakan type: Subintimal edema

### Clinical Picture

#### A) Acute stage

- Hepatomegaly: Marked, firm, smooth, tender
- No splenomegaly
- Ascites: Rapidly-accumulating with ↑↑ protein content
- Dilated abdominal veins

#### B) Subacute & chronic stage

- Liver ↓↓ in size
- Splenomegaly
- Dilated abdominal veins
- Liver cirrhosis (portal HTN & LCF)

### Investigations

- LFT
- Investigation of portal HTN
- Paracentesis & ascitic fluid examination: Transudate with ↑↑ protein content

### Treatment

- Supportive
- Rx of portal HTN

## Budd-Chiari Syndrome

### Definition

Posthepatic portal HTN due to obstruction of the hepatic veins

### Etiology

- ☒ Idiopathic
- ☒ Thrombosis: SLE, polycythemia, Behcet's...

### Clinical Picture

#### A) Acute form

- Hepatomegaly: Marked, firm, smooth, tender
- No splenomegaly
- Ascites: Rapidly-accumulating with ↑↑ protein content
- Dilated abdominal veins

#### B) Chronic form

- Hepatomegaly: Mild to moderate, firm, smooth
- Splenomegaly

### Investigations and Treatment

# Hepatic Encephalopathy

## Definition

Neuropsychiatric syndrome occurring in patients with severe liver disease ( $\pm$  P/S shunts)

## Pathogenesis

- A) Production of toxic substances
  - Ammonia (*mechanism?*)
  - GABA
  - Mercaptans
  - Benzodiazepine-like substances
- B) Formation of false neurotransmitters "Disturbances of amino acids"
- C)  $\uparrow\uparrow$  Permeability of BBB
- D) Hypokalemia & Alkalosis

## Precipitating Factors

1.  $\uparrow\uparrow$  Protein intake
2. GIT bleeding
3. Infection
4. Trauma & surgery
5. Vomiting, diarrhea & constipation
6. Drugs: Diuretics, sedatives, ammonium chloride
7. Paracentesis
8. Transfusion of stored blood

## Clinical Picture (4 Stages)

	I	II	III	IV
<b>Symptoms</b>	<b>Lethargy</b> Inverted sleep rhythm	<b>Confusion</b> Disorientation Inappropriate behavior	<b>Stupor</b>	<b>Coma</b> IVa: respond to pain IVb: No response
<b>Signs</b>	# Drawing figures # Mental tasks	Fetor hepaticus Asterixis	Hyperreflexia Asterixis	Areflexia No Asterixis
<b>EEG</b>	Normal	Generalized slowing	Markedly abnormal	Markedly abnormal Or silence

## Treatment

1. Diet
  - Protein restriction
  - Adequate caloric intake ( $\uparrow\uparrow$  CHO)
2. Stomach wash
3. Rx of GIT bleeding
  - H<sub>2</sub> blockers
  - Vitamin K
  - FFP
4. Lactulose (Oral or NGT): 10-50cc every 2-4 hrs
5. Enema every 6 hrs (Lactulose enema can be used)
6. Locally-acting antibiotics: Neomycin (50-100 mg/kg/day NGT every 6 hrs)
7. rimazole (benzodiazepine antagonist)
8. Care of the comorbid
9.  $\uparrow\uparrow$  support & transplant

### Action of Lactulose:

1. Lactic acid ( $\downarrow\downarrow$  production of ammonia)
2. Lactic acid ( $\downarrow\downarrow$  Absorption of ammonia)
3. Osmotic diarrhea ( $\downarrow\downarrow$  intestinal toxins)

### Use of Neomycin

100 mg/kg/day

# Fulminant Hepatic Failure

## Definition

**Acute liver cell failure** with **encephalopathy** developing in less than 8 weeks in a patient without pre-existing liver disease

## Criteria of Diagnosis

1. Absence of chronic liver disease
2. Acute liver failure (< 8 wks duration)
3. Coagulopathy (INR > 2 not corrected by Vit. K OR INR > 1.5 with encephalopathy)

## Etiology

1. Infection: Hepatitis (A, B, C, D), CMV, EBV, Sepsis
2. Drugs & toxins
  - ☒ Predictable (Dose-related): Carbon tetrachloride, Acetaminophen, MTX, Mushroom
  - ☒ Idiosyncrasy (Not dose-related): INH, Na valproate
3. Hepatic ischemia & hypoxia
  - ☒ Sepsis, shock & HF
  - ☒ Congenital heart disease
4. Metabolic diseases
  - ☒ Galactosemia
  - ☒ Hereditary fructose intolerance (↓↓ Aldolase B)
  - ☒ Tyrosinemia
  - ☒ NISD
  - ☒ Wilson disease
  - ☒ Mitochondrial hepatopathies
  - ☒ FA oxidation defects
5. Reye syndrome

**N-acetylcysteine**

## Pathology

- Massive liver cell necrosis
- Centilobular necrosis: Paracetamol
- Steatosis: Na Valproate
- Acute hepatitis: INH
- Fibrosis: MTX
- Reye syndrome: Fatty infiltration

### Patterns of hepatic drug injury:

- **Biliary sludge:** Ceftriaxone
- **Hepatic adenoma:** OCPs
- **VOD:** Irradiation + Cyclophosphamide
- **Cholestasis:** Erythromycin

## Pathophysiology

- Hypoalbuminemia
- Hypoglycemia
- Coagulopathy (↑↑ PT, ↑↑ INR)
- Acid-base disturbances: Metabolic acidosis & respiratory alkalosis. Why?
- Electrolyte disturbances: Hyponatremia & hypokalemia
- Hyperbilirubinemia (except in Reye syndrome)
- Hepatic encephalopathy (↑↑ Ammonia...)
- Hepatorenal syndrome
- Brain edema. Why?

## Clinical Picture Acute liver cell failure + Pathophysiology

## Investigation Acute liver cell failure + Pathophysiology + LFT

Liver enzymes: ↑ ALT  
 ↑↑ ALP & γ-GT with the severity of LFT  
 Bilirubin ↑↑ & prolonged PT

## Management of Fulminant Hepatic Failure

### A) Monitoring (ICU)

#### 1. Clinical

- Vital signs
- Conscious level, convulsions
- Bleeding, Urine output & Infection

#### 2. Laboratory

- Liver function tests & ammonia
- KFTs, Electrolytes, ABG

**Sedatives should be avoided**

### B) Management

#### 1. Respiratory support (O<sub>2</sub> therapy, ETT, mechanical ventilation)

#### 2. Fluid therapy

- Target: Normovolemia with normal UOP, blood glucose & electrolytes
- Type of fluid: Glucose : NS (4:1) + Potassium supplementation
- Albumin 20% is indicated in severe hypoalbuminemia
- Volume: 70% of maintenance (Brain edema)

#### 3. Nutrition

- NGT
- TPN

#### 4. Prevention & Rx of hepatic encephalopathy

#### 5. Rx of bleeding (How?)

#### 6. Rx of brain edema (Rapidly-acting measures??)

#### 7. Control of infection

#### 8. Hepato-renal syndrome

- Keep the patient normovolemic
- Induction of diuresis (Mannitol or furosemide)

#### 9. Rx of ascites

- Fluid restriction
- Mild diuretics (K-sparing e.g., spironolactone)
- Paracentesis is indicated only if there is significant mechanical compression, why?

#### 10. Dramatic measures

- a. Charcoal hemoperfusion
- b. Exchange transfusion
- c. Plasmapheresis
- d. Hemodialysis
- e. Crossed circulation with human volunteer or animal
- f. Liver transplantation

### Prognosis

- Mortality is 70%
- Cause of death: Brainstem herniation
- Poor prognosis with: Age < 1yr, stage 4 encephalopathy, need for dialysis





# Chronic Hepatitis

## Definition

It is chronic inflammatory liver disease

Chronicity > 3-6 m

## Etiology

1. Viral hepatitis (B, C, D)
2. Autoimmune hepatitis
3. Metabolic (Galactosemia, Tyrosinemia, NISD, CF, Wilson,  $\alpha$ -1-AT  $\downarrow\downarrow$ , Niemann-Pick)
4. Drug-induced (INH, methyl dopa, MTX)

90% of HBV infection in the 1<sup>st</sup> yr becomes chronic

## Pathology

- Inflammatory cell infiltration in the portal tracts
- Variable degrees of liver cell necrosis
  - Piecemeal necrosis
  - Bridging necrosis (Porto-portal or porto-central)
- Progression to cirrhosis may occur

Classification into active vs. persistent hepatitis is not useful as once thought

## Investigations & Treatment ➡

HBV:  $\alpha$ -Interferon (SC 3/wk)  $\pm$  Lamivudine  
HCV:  $\alpha$ -Interferon + Ribavirin

# Autoimmune Hepatitis

## Definition

It is chronic inflammatory liver disease characterized by  $\uparrow\uparrow$  liver enzymes, liver-associated autoantibodies & hypergammaglobulinemia

## Etiology

Immune process in a genetically predisposed individual

## Pathology

- Inflammatory cell infiltration in the portal tracts
- Variable degrees of liver cell necrosis
  - Piecemeal necrosis
  - Bridging necrosis (Porto-portal or porto-central)
- Progression to cirrhosis may occur

## Clinical Picture ( $\text{♀} > \text{♂}$ )

### A) Hepatic

- Constitutional: FHAM
- Manifestation of liver disease: Jaundice, bleeding, HSM...

### B) Extra-hepatic

- Arthritis, nephritis, hemolytic anemia, thyroiditis



## Investigations

1. LFT (Albumin, PT, bilirubin) may be impaired
2.  $\uparrow\uparrow$  ALT & AST (Normal ALP & GGT except in...)
3. Hypergammaglobulinemia
4. Autoantibodies: ANA, LKM antibodies, Anti-smooth muscle Ab
5. Exclusion of other causes of chronic hepatitis (e.g., Hepatitis B, C, D)

## Treatment

Steroids  $\pm$  Azathioprine

# Mitochondrial Hepatopathies

## Definition

Defects in hepatic mitochondrial functions

OXPHOS

## Classification

A) **Primary:** Mutation in either nDNA or mtDNA

B) **Secondary:** Mitochondrial disease 2ry to exogenous factor (e.g., Reye \$, drugs...)

## Clinical Picture

A) **Primary**

- Abdominal pain, anorexia, diarrhea, constipation
- Acidosis, hypoglycemia, seizures
- Liver manifestations: Cholestasis, hepatomegaly, FHF

B) **Secondary:** Picture of the cause (Reye syndrome)

### 1ry Mito. hepatopathies:

1. Respiratory chain defects
2. Carnitine deficiency &  $\downarrow\downarrow$  CPT
3. Urea cycle defects
4. FA oxidation defects

**Investigations**  $\uparrow\uparrow$  Serum & CSF lactate +  $\uparrow\uparrow$  Lactate / Pyruvate ratio + Muscle biopsy

**Treatment** Supportive +  $\uparrow\uparrow$  Dietary Carbohydrates + Cocktails

## Reye syndrome

### Definition

- ☒ Encephalopathy
- ☒ Fatty degeneration of the liver
- ☒ No known explanation

Prevalence of Reye \$ is  $\downarrow\downarrow$ , why?

### Etiology

Interaction of **Viral infection** (Influenza, Varicella) & **Salicylate** use in a **Genetically** predisposed individual

### Pathogenesis

Impaired mitochondrial function & mitochondrial enzymes (OTC, CPS)  $\rightarrow$   $\uparrow\uparrow$   $\text{NH}_3$

### Clinical Picture

- Preceding viral infection
- Acute onset of vomiting & Encephalopathy
- Clinical staging of Reye syndrome

I	II	III	IV	V
Lethargy Vomiting	Confusion Hyperreflexia Hyperventilation	Light coma Seizures Decorticate	Deep Coma Decerebrate	Deep Coma (Apnea) Decerebrate or flaccidity Dilated fixed pupil Isoelectric EEG

### Investigations

1.  $\uparrow\uparrow$  ALT & AST (Not ALP)
2.  $\uparrow\uparrow$  PI
3. Hyperammonemia
4. Normal bilirubin level (Anicteric)
5. Hypervolemia

### Treatment

1. Ammonia  $\rightarrow$   $\downarrow\downarrow$

### Reye-like conditions:

1. Metabolic
  - Respiratory chain defects
  - Carnitine deficiency &  $\downarrow\downarrow$  CPT
  - Urea cycle defects
  - FA oxidation defects
  - Organic acidemia
2. Drugs (Valproate, Aspirin)
3. CNS infection (Meningitis)
4. Encephalopathy

# Cystic Diseases of the Biliary Tract & Liver

## Choledochal Cyst

### Definition

Congenital saccular or fusiform dilatations of the CBD  
It may be associated with Caroli disease

### Etiology

- ☒ Congenital malformation
- ☒ Reflux of pancreatic enzymes into the CBD

### Clinical Picture

- A) **Infancy:** Cholestasis, LCF  
B) **Childhood:** Triad of...



**Complications** Cholangitis [fever, rigors, abdominal pain, jaundice, tender liver]

**Investigations** US, CT, MRI

**Treatment** Surgical excision (+ Roux-en-Y choledochojejunostomy)

## Caroli Disease

(Cystic Dilatation of Intrahepatic Bile Ducts)

### Definition

Congenital multiple saccular dilatations of the Intrahepatic bile ducts (AR)  
It may be associated with choledochal cyst

### Pathology

The dilated bile ducts are in continuity with the main duct system

- **Caroli disease:** Isolated IHBD dilatation
- **Caroli syndrome\*:** Caroli disease + ARPKD + Congenital hepatic fibrosis

### Clinical Picture

- A) **Caroli disease:** Attacks of Cholangitis  
B) **Caroli syndrome:** Attacks of Cholangitis + Portal HTN + HSM + Renal masses

**Complications** Cholangitis & Calculi formation

### Investigations

- ↑↑ Direct bilirubin, ↑↑ ALP, CBC (Leukocytosis)
- US, CT, MRI

### Treatment

- Medical: Antibiotics for cholangitis
- Surgical: for calculi (?partial hepatectomy)

## Congenital Hepatic Fibrosis

### Definition

AR disorder characterized pathologically by peri-portal fibrosis  
It may be associated with choledochal cyst & Caroli disease

**Clinical Picture** HSM + Portal HTN ± Cholangitis

75% have renal disease (ARPKD\*)

**Investigations** LFT (Normal), Investigation of portal HTN + US + Liver biopsy

**Treatment** Rx of portal HTN (sclerotherapy)

**Prognosis** Portal HTN & Renal disease (ARPKD\*)

## ARPKD & ADPKD

	ARPKD (Infantile)	ADPKD (Adult)
<b>Genetics</b>	AR <sup>6</sup>	AD <sup>16</sup>
<b>Prevalence</b>	1:10,000	1:1000
<b>Pathology</b>	Renal enlargement Microscopic cysts Cysts are dilatation of the collecting tubules Liver: periportal fibrosis (100%) Bile duct proliferation & Caroli's disease	Renal enlargement Larger cysts Cysts develop from all nephron regions
<b>Affected Organs</b>	Kidneys & Liver only	Kidneys & Extra-renal (Liver, brain, GIT)
<b>Clinical Picture</b>	<i>Depend on the age of onset:</i> <b>A) Fetal:</b> Oligohydramnios <b>B) Neonatal:</b> ▪ Bilateral flank masses ▪ Pulmonary hypoplasia (RD) ▪ Potter facies: flat nose, micrognathia, low-set ears, limb-positioning defects ▪ HTN, renal failure <b>C) Infantile</b> ▪ Renal failure ▪ HSM <b>D) Childhood</b> ▪ HSM, portal hypertension, GIT bleeding (hematemesis & melena), hypersplenism ▪ CRF	May be asymptomatic ▪ Onset: 30-50 yrs (may in neonates) ▪ Hematuria ▪ Flank pain, flank masses ▪ HTN ▪ Extrarenal manifestations: ☑ Intracranial aneurysms, SAH ☑ Hepatic cysts ☑ Intestinal diverticuli ☑ Mitral valve prolapse ▪ ESRD (50-70 yrs)
<b>Investigations</b>	Available	
<b>Dagnosis</b>	▪ Lab: KFT, electrolytes, LFT, CBC ▪ U/S (markedly enlarged, echogenic, poor C/M differentiation, No cysts ...) ▪ Invasive: Liver & Renal biopsy Upper GIT endoscopy	▪ Lab: KFT, electrolytes, LFT, CBC ▪ U/S (enlarged kidneys, macrocysts ...) U/S may be normal in 20% by 20 yrs ▪ Invasive: Renal biopsy
<b>Treatment</b>	▪ Supportive (HTN, fluid ...) ▪ Respiratory care ( <i>mechanical ventilation</i> ) ▪ Renal replacement therapy (Dialysis, RT) ▪ Liver support (Rx of Portal HTN)	▪ Supportive ▪ Control of HTN (ACE inhibitors*) ▪ Renal replacement therapy
<b>Prognosis</b>	Neonatal mortality = 30% >50% develop ESRD during the 1 <sup>st</sup> decade	Neonatal 50% develop ESRD at 50-70 yrs

## Cholelithiasis

### Etiology

- Chronic hemolytic anemia
- Obesity
- Heat disease or resection
- Prolonged fasting
- Cystic fibrosis
- Prolonged TPN

Types – Pigment stones (Heme-saponates & Cholesterol (Radio-labeled))

# Ascites

## Definition

Accumulation of fluid in the peritoneal cavity

## Etiology

### A) Portal HTN

### B) Hypoalbuminemia

- Liver cell failure
- Nephrotic syndrome
- Malabsorption (Protein-losing enteropathy)

### C) Peritoneal diseases

#### a. Peritonitis

- Acute peritonitis (Fever, abdominal pain & tenderness)
- TB peritonitis (Loss of weight, diarrhea, doughy abdomen)

#### b. Malignancy

- Lymphoma
- Neuroblastoma

### D) Chylous

- Congenital lymphatic malformation
- Thoracic duct injury (Trauma or surgery)
- Lymphatic obstruction (LN, masses, bands)

### Diagnosis of chylous ascites depends on:

- Paracentesis after fat-containing meal
- Ascitic fluid: ↑↑ TAG, Lymphocytes & Ptn

### E) Urinary ascites

### F) Biliary ascites

## Clinical Picture Inspection + Palpation + Percussion + Auscultation

## Investigations

- Investigations of the cause
- SAAG
- Paracentesis & ascitic fluid examination (Physical, Chemical, Cytological & Bacteriological)
  - Physical: Clear in transudate, turbid in others
  - Cytological: ↑↑ PNLs (Peritonitis), ↑↑ Lymphocytes (TB), Malignant cells
  - Chemical: Milky fluid with ↑↑ TAG (Chylous), Blood-stained (Tumors), Urine, Bile
  - Bacteriological: Culture of ascitic fluid

	Transudate	Exudate
Aspect	Clear	Turbid
Specific gravity	Low (< 1015)	High (> 1015)
Proteins	Low (< 2.5 g/dl)	High (> 2.5 g/dl)
Cell Number	Few (< 1000 /mm <sup>3</sup> )	Many (> 1000 /mm <sup>3</sup> )
Cell Type	Lymphocytes	PNLs
LDH	Low (< 200 IU/L)	High (> 200 IU/L)

## Treatment

- Rx of the cause
- Monitoring of BW, hydration state, urine output, electrolytes
- Diet: Salt, fluid & protein restriction + K supplementation
- Diuretics: Spironolactone\* or furosemide
- Salt-free anionmin. diuretics
- Abdominal paracentesis combined with salt-free anionmin. in tense ascites (caution: ↓↑↑)
- Regional or systemic venous drainage + treatment of obstruction & repts

# Neonatal Cholestasis

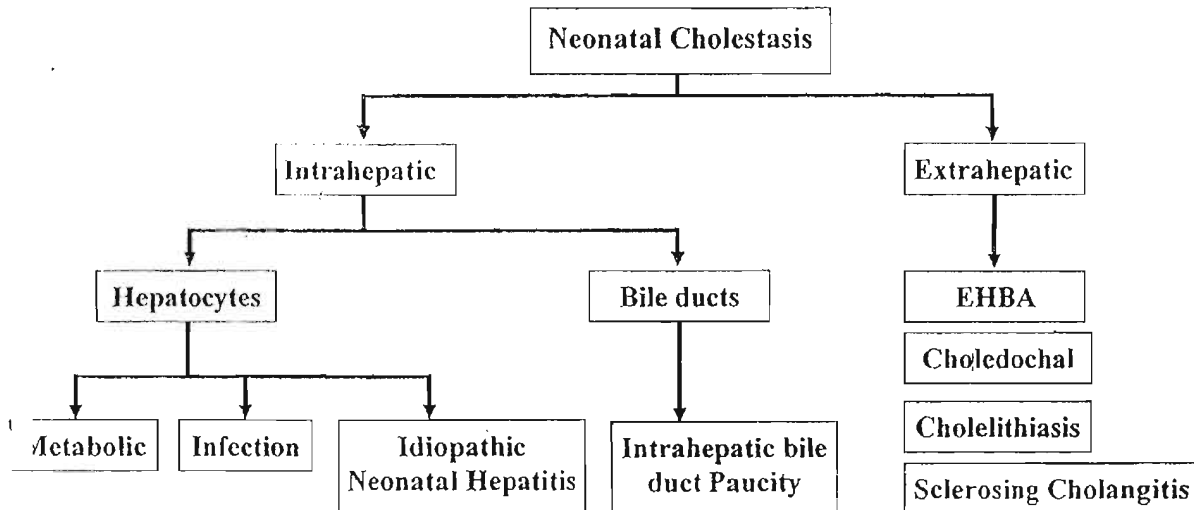
## Definition

**Cholestasis:** Any condition in which there is retention of substances normally excreted in bile with appearance of bile within the elements of the liver usually associated with 2ry liver cell injury [Practically, direct bilirubin > 2 mg% or > 20% of total bilirubin]

**Neonatal Cholestasis:** Cholestasis that persists > D14 [Always pathological]

**Obstructive jaundice:** Cholestasis due to mechanical obstruction in the hepatobiliary system

## Etiology



### A) Infections

- Neonatal sepsis
- TORCH infection
- UTI
- CMV, EBV, hepatitis viruses

### B) Metabolic

- Galactosemia
- Tyrosinemia
- $\alpha$ -1-Antitrypsin deficiency
- Cystic fibrosis
- Gaucher & Niemann-Pick
- Zellweger \$ (Cerebrohepatorenal)
- Neonatal Iron storage Disease (NISD)
- Mitochondrial hepatopathies
- Dubin-Johnson syndrome & Rotor syndrome
- Aagaens: Cholestasis + Lymphedema

### C) Cholestasis associated with TPN (Discuss)

### D) Inspissated bile syndrome (Post-hemolytic cholestasis)

### E) Bile acid synthetic defects

- Reductase
- Dehydrogenase

### F) Progressive familial intrahepatic cholestasis (PFIC)

- PFIC 1 (Byler disease):  $\downarrow\downarrow$  GGT
- PFIC 2:  $\downarrow\downarrow$  GGT
- PFIC 3:  $\uparrow\uparrow$  GGT

### G) Idiopathic neonatal hepatitis (Most common)

### H) Paucity of intrahepatic bile ducts (= Intra-hepatic biliary hypoplasia)

- a. Non-syndromic
- b. Syndromic (Alagille syndrome = Arteriohepatic dysplasia)
  - Etiology: AD (with reduced penetrance)
  - Pathology:  $\downarrow$  intra-hepatic bile ducts
  - Diagnosis

### I) Extrahepatic EHBA

#### Alagille:

1. Intrahepatic paucity (100%)
2. Vertebral arch defects
3. Abnormal facies (Prominent forehead, Hypertelorism, deep set eye)
4. Ocular (Posterior embryotoxon)

## Pathology

### A) Nonspecific changes

- Accumulation of bile within the hepatocytes
- Liver cell injury & degeneration
- Giant cell transformation
- Infiltration with inflammatory cells
- Bile duct proliferation
- Fibrous bands (Intact hepatic architecture)

### B) Specific changes

- Idiopathic Neonatal hepatitis: Marked infiltration with mononuclear cells
- EHBA: Marked bile duct proliferation
- Galactosemia & hereditary fructose intolerance: Pseudoacinar formation
- $\alpha$ -1-Antitrypsin deficiency: PAS +ve granules
- Paucity of intrahepatic bile ducts: Bile ducts/Portal tracts ratio  $< 0.6$  [Normally = 0.9-1.8]

## Pathophysiology

### A) Bile pigments $\downarrow\downarrow$ in intestines

- $\downarrow\downarrow$  Stercobilinogen  $\longrightarrow$  Pale stools (Clay-colored in EHBA)
- $\downarrow\downarrow$  Urobilinogen

### B) Bile pigments $\uparrow\uparrow$ in blood

- Jaundice
- Dark-colored urine

### C) Bile salts $\downarrow\downarrow$ in intestines

- Defective fat digestion
- Defective fat absorption (Steatorrhea)

### D) Bile salts $\uparrow\uparrow$ in blood

- Bradycardia
- Pruritus

Vit A: Thick skin  
Vit D: Rickets & osteoporosis  
Vit K: Bleeding  
Vit E: Hemolytic anemia, PN, myopathy

### E) Cholesterol $\uparrow\uparrow$ in blood: Xanthomas

### F) Biliary cirrhosis

- Liver cell failure
- Portal hypertension

## Clinical Picture

- Pathphysiology (Bradycardia, scratch marks...)
- Color of urine & stools
- HSM
- Manifestations of vitamin deficiencies
- Manifestations of congenital infection
- Cardiac murmur
- Ocular
- Lymphedema
- Abdominal mass

## Investigations

### A) Laboratory


- ☒ Liver function tests (Liver enzymes, albumin, Bilirubin, PT, INR...)
- ☒ Reducing substances in urine
- ☒ Urine succinylacetone
- ☒ TORCH
- ☒ Serum & urine aminogram
- ☒ Sweat chloride test
- ☒  $\alpha$ -1-Antitrypsin

**TCT**

#### Value of US:

1. Diagnosis of choledochal cyst
2. TC sign: suggests EHBA
3. Visualization of GB

### B) Imaging

- ☒ Abdominal US 
- ☒ CT, MRI: choledochal cyst
- ☒ Scintigraphy (Tc): "Not practical"

**TC sign: suggests EHBA**

### C) Invasive

- ☒ Duodenal aspirate: ?Bile-stained fluid
- ☒ Liver biopsy

**Liver biopsy is the most important procedure in diagnosis of neonatal hepatobiliary diseases**

## Extrahepatic Biliary Atresia

### Incidence

It is the 2<sup>nd</sup> most common cause of neonatal cholestasis

### Terminology

The term, biliary atresia is not accurate.

A more correct name is **progressive obliterative cholangiopathy**

### Definition

85% have the atretic segment at or above the porta hepatis

15% have distal atretic segment with patent extrahepatic CBD up to the porta hepatis

### Etiology

EHBA has postnatal onset (? infectious etiology; Reovirus)

EHBA has progressive course (ascending). This explains the high failure rate of "Kasai"

### Clinical Picture

- Clay-colored stools (pigmented stools can be detected in the first few days)
- Consistently pigmented stools is against the diagnosis

### Investigations

1. as before
2. Liver biops
3. Duodenal aspirate: No bile-stained fluid

**Early Diagnosis is critical!**

### Treatment

#### A) Medical Rx

#### B) Surgical Rx: Kasai operation (Transection of the porta hepatis + anastomosis to the bowel)

##### • Postoperative management

- Antibiotics: Cefotaxime (100 mg/Kg/day)
- Antipyretics: Paracetamol (10-15 mg/Kg/dose), PO, Rectal, IV
- Steroids: Hydrocortisone followed by oral Prednisolone (1mg/Kg/day)

**Avoid Ceftriaxone**

##### • Post-Kasai fever

It is a common complication of Kasai operation. It is caused by the release of endotoxin from the bacteria in the gut. It is usually self-limiting and resolves within 24-48 hours. It is treated with antibiotics and antipyretics.



## Management of Neonatal Cholestasis

### **A) Medical**

1. Nutrition: Formula containing medium-chain triglycerides (Pregestimil)
2. Fat-soluble vitamins
  - **Vit A:** 50.000 IU twice weekly
  - **Vit D:** 300.000 IU/ 2 months (Check urine Ca/Cr ratio)
  - **Vit K:** 10 mg/week PO (Use MM ampoules)
  - **Vit E:** 100 IU/day
3. Water-soluble vitamins: supplementation with twice the RDA
4. Micronutrient supplementation: Ca, P, Zn
5. Choleretics: Ursodeoxycjolic acid (Ursofalk): 15-30 mg/Kg/day single daily dose
6. Pruritus
  - Ursodeoxycjolic acid
  - Cholestyramine (4-16 g/day)
  - Rifampicin
  - Phenobarbitone
  - Carbamazepine
  - Cool baths, topical creams, anti-histamines
7. Management of complications: portal hypertension, LCF
8. Liver transplantation

Vitamin K is the initial Rx of cholestasis

### **B) Surgical**

1. Excision of choledochal cyst
2. Kasai operation

# Liver Biopsy

## Definition

Liver tissue is obtained for histological &/or enzymatic analysis

## Indications

1. Neonatal cholestasis
2. Chronic hepatitis
3. Metabolic liver disease e.g., galactosemia...
4. Unexplained hepatomegaly
5. Reye's syndrome
6. Congenital hepatic fibrosis
7. Enzyme analysis (e.g., GSD...)
8. Storage diseases (e.g., Wilson, hemochromatosis, NISD...)
9. Drug toxicity (e.g., MTX, INH, antimetabolites, anticonvulsants...)

Liver biopsy is the most common and precise method for diagnosis of neonatal hepatobiliary diseases

Liver biopsy can be performed safely in infants as young as 1 wk of age

## Preparation

- Revise indications
- Hb > 8 g %
- Platelets > 60.000/mm<sup>3</sup>
- PC > 60% (PT within 3 sec of normal)
- Abdominal US
- IV line
- IM Vitamin K
- Fasting for 2 hrs

## Contraindications

- ☒ Bleeding tendency (PT, Platelet...)
- ☒ Suspected vascular, cystic or infectious lesions
- ☒ Severe ascites

## Methods

- ☒ Percutaneous\* (US or CT guided)
- ☒ Laparoscopic
- ☒ Transjugular approach
- ☒ Open (Laparotomy)

## Procedure

- US or CT guided
- Conscious sedation + LA
- The amount of tissue obtained is usually sufficient

## Post-biopsy care

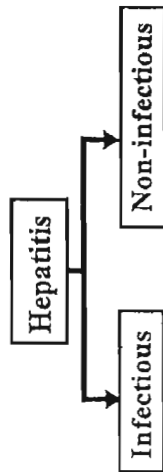
- Place the patient on his Rt side
- Vital signs every 30 min (2 hrs), every 1 hr (2 hrs) then every 2 hrs
- If bleeding is suspected IV fluids + Hb% ± blood transfusion + US

## Complications (Rare)

- Hemorrhage
- AV fistula
- Pneumothorax
- Infection
- Bile peritonitis

## Examination

# Viral Hepatitis



## Definition

Inflammation of the liver by viruses

## Classification

- A) Hepatotropic viruses: HAV, HBV, HCV, HDV, HEV [Hepatitis is the primary disease manifestation]  
 B) Non-Hepatotropic viruses: CMV, EBV, Rubella, HIV [Hepatitis can occur as part of their C/P]

## Features

	HAV	HBV	HCV	HDV	HEV
Type of the virus	Enterovirus	Hepadnavirus	Flavivirus	Defective virus??	Calicivirus
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Transmission	Feco-oral	Parental-Sexual Vertical	Parental-Sexual	Parental-Sexual	Feco-oral
Incubation period	2-6 wk	2-6 months	1-6 months	20-90 days	2-9 wk
Carrier state	No	Yes	Yes	Yes	No
Chronicity	No	Yes	Yes	Yes	No
Infrequent disease	Rare	Yes	Rare	Yes	Yes
Diagnostic test	Anti-HAV Ab (IgM)	HBsAg, Anti-HBc (IgM)	Anti-HCV Ab, PCR	Anti-HDV Ab	Anti-HEV Ab
Mortality (Acute)	0.1 %	1 %	1-2 %	2-20 %	1-2 %
Prevention	<ul style="list-style-type: none"> <li>Health education</li> <li>Hand washing</li> <li>Food sanitation</li> <li>Isolation for 1wk (After onset of jaundice)</li> </ul>	<ul style="list-style-type: none"> <li>Health education</li> <li>Screening of blood &amp; blood products</li> <li>Disposable needles &amp; syringes</li> <li>Proper sterilization of Dental &amp; surgical instruments</li> </ul>	As HAV		
Vaccine	Yes Inactivated vaccine IM, 2 doses (0.5 ml) 5 months interval	Yes Recombinant vaccine IM, 3 doses (0.5 ml) 2, 4, 6 months	No	Yes (HBV)	No
Treatment	No	α-Interferon = Lamivudine	α-Interferon + Ribavirin	α-Interferon	No

## Diagnosis of Viral Hepatitis

### I) Clinical Forms of acute hepatitis

#### **1. Icteric hepatitis [3 Stages]**

##### **a. Pre-icteric stage (4-6 days)**

- FHAM
- Abdominal pain & Vomiting
- Dark-colored urine (Bilirubinuria): in the last 1-3 days

##### **b. Icteric stage (2-4 wks)**

- Jaundice
- Dark-colored urine & pale stools
- Tender hepatomegaly
- Improvement of the constitutional manifestations (anorexia may continue)

##### **c. Convalescence stage**

- Gradual improvement (Jaundice & hepatomegaly)

#### **2. Cholestatic hepatitis**

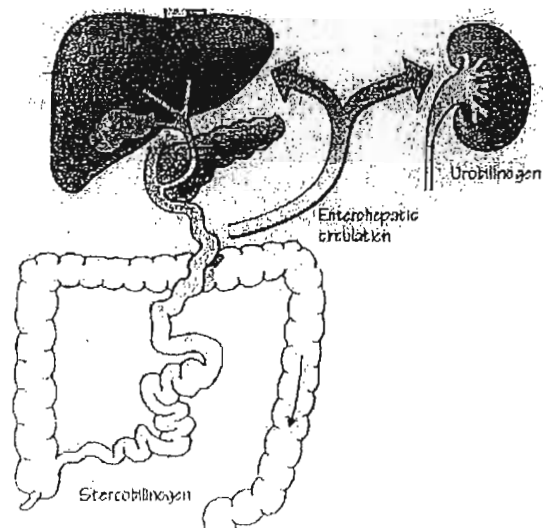
- Marked bile duct obstruction
- Marked pruritis
- Dark-colored urine & clay-colored stools

#### **3. Anicteric hepatitis**

- Constitutional manifestations
- No jaundice
- More common in infants

#### **4. Fulminant hepatitis (Most serious)**

- Acute liver cell failure
- Rapidly-developing coma



### II) Investigations of acute hepatitis

#### **1. To prove acute hepatitis**

- Serum bilirubin: Mild (2-6 mg %), Moderate (6-10 mg %), Severe (> 10 mg %)
- Liver enzymes (ALT, AST): Markedly ↑↑ "hundreds-thousands"
- Urine analysis: Bilirubinuria

#### **2. Fulminant hepatitis**

- Serum bilirubin > 10 mg %
- Serum albumin < 3 gm%
- Prothrombin time > 20 seconds
- Ammonia > 150  $\mu$ g %
- Hyponatremia, Hyponatremia & Metabolic acidosis

### III) Diagnosis of the causative virus

#### 1. Clinical differentiation (See table)

- Onset: Acute (HAV), insidious (HBV, HCV, HDV)
- Course: Short (HAV), prolonged (HBV, HCV, HDV)

#### 2. Laboratory differentiation (Hepatitis markers)

##### a. Hepatitis A

- Anti-HAV IgM: Recent infection
- Anti-HAV IgG: Previous infection (Immunity)

##### b. Hepatitis B

- **HBsAg:**  
Infection [HBsAg persistence = Chronicity or carrier state]
- **Anti-HBs:**  
Recovery & Immunity
- **HBcAg:**  
Not present in serum (liver biopsy)
- **Anti-HBc IgM:**  
Recent infection
- **Anti-HBc IgG:**  
Chronicity
- **HBeAg:**  
High infectivity
- **Anti-HBe:**  
Low infectivity
- **HBV-DNA:** PCR

Anti-HBc IgM may be the **only** indicator of recent HBV infection "Window phase"

**Diagnosis of HBV infection:**

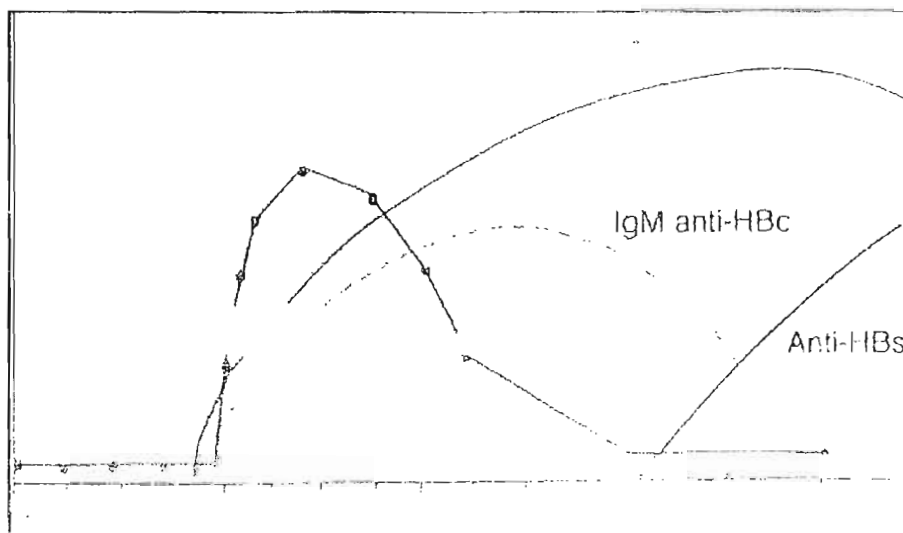
1. **Acute:** HBsAg, Anti-HBc IgM
2. **Immunity:** Anti-HBs Ab
3. **Chronicity:** Persistent HBsAg, Anti-HBc IgG

##### c. Hepatitis C

- **Anti-HCV Ab:**  
Exposure to the Infection (Not immunity)
- **HCV-RNA:** PCR

##### d. Hepatitis D & E

- **Anti-HDV Ab & Anti-HEV Ab:**  
Recent Infection (IgM)  
Previous infection (IgG)



# Immunology

## Function of the Immune System

Prevention or limitation of infections by microorganisms (bacteria, viruses, fungi & parasites)

## Types of Immunity

### A) Innate (Non-specific)

#### 1. First line (Barriers)

- ☒ **Mechanical:** Intact skin, mucosa, hair, tears
- ☒ **Chemical:** HCl, sweat
- ☒ **Biological:** Normal intestinal flora

#### 2. Second line

- ☒ **Bactericidal substances:** Lysozyme, complement, acute phase reactants, INF
- ☒ **Phagocytosis**
- ☒ **Natural killer (NK):** CD16, CD56 (No CD3)

#### Acute phase reactants

- CRP
- $\alpha$ -1-AT
- Ceruloplasmin
- Fibrinogen

Lysozyme dissolves C.W.

### B) Acquired (specific) [Specific – Self/non-self – Diversity – Memory]

#### 1. Humoral Immunity

- ☒ B-lymphocytes (CD19)
- ☒ Antibodies (immunoglobulins)

#### 2. Cell mediated immunity

- ☒ T-lymphocytes (CD3)
- ☒ Direct or through Cytokines

## Phagocytosis

### Definition

It is the capture, ingestion & destruction of invading microorganisms by Phagocytes ??

### Steps

1. Chemotaxis (C5a, IL): Migration to site of infection
2. Ingestion (phagosome  $\rightarrow$  phagolysosome)
3. Digestion (Intracellular killing)
  - O<sub>2</sub>-dependent (superoxide O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, hypochlorous acid HOCl)
  - O<sub>2</sub>-independent (proteolytic & hydrolytic enzymes)
4. Antigen presentation (in association with MHC II)
5. Macrophages secrete IL-1, IL-6, TNF

**Opsonization:**  $\uparrow\uparrow$  Phagocytosis if the organism is coated with Ab or C3b

Antigen presenting cells

## Lymphocytes

### 1. B-Lymphocytes (30%)

- **Site:** Circulation, LN, spleen
- **Surface markers:** MHC II, CD19
- **Function:** B-Lymphocytes  $\rightarrow$  Plasma cells  $\rightarrow$  Antibodies

### 2. T-Lymphocytes\* (60%)

- **Site:** Circulation
- **Surface markers:** TCR-CD3 and either CD4 or CD8
- **Function:**
  - CD4 [= T-Helper (T<sub>H</sub>)]
  - T<sub>H</sub> recognize antigens on APC (in association with MHC II)
  - CD8 [= T-cytotoxic (T<sub>c</sub>) & ??T-suppressor (T<sub>s</sub>)]
  - T<sub>c</sub> recognize antigens on cells (in association with MHC I)

### 3. NK (10%)

TCR = T cell receptors

T<sub>H0</sub> Precursor  
T<sub>H1</sub> Bacterial & viral  
T<sub>H2</sub> Allergy

**MHC-I** present on all nucleated cells  
**MHC-II** present on APCs

## Complement

### Definition

Complement system is a complex enzymatic system composed of 20 proteins

### Activation

#### 1. Classic Pathway

- **Stimulus:** Antigen-Antibody complexes
- **Cascade:** C1 → C4 → C2 → C3 → C5b6789 (Membrane attack unit)

#### 2. Alternate Pathway (Bypass C<sub>1,4,2</sub>)

- **Stimulus:** Bacterial polysaccharides & endotoxins (No antibody)
- **Cascade:** C3 → C5b6789 (Membrane attack unit). Activation involves properdin system

#### 3. Lectin Pathway

### Regulation

- ☒ Short half-life
- ☒ Serum Inhibitors e.g., C1 & C6 inhibitors

Congenital ↓↓ C1 inhibitor causes hereditary angioneurotic edema

### Biological Activities

1. Cytolysis: C5b6789 (Membrane attack unit)
2. Chemotaxis: (C5a)
3. Opsonization: (C3b)
4. Anaphylatoxins (C3a, C4a, C5a) → mast cell degranulation → Release of mediators
5. ↑↑ Phagocytosis: (C5a)
6. ↑↑ Antibody production: (C3b)
7. Immune clearance: (C3b)

Complement deficiency is associated with immune complex diseases

## Cytokines

### Definition

They are low MW proteins that regulate the amplitude & duration of the immune response

### Examples

1. IL-1 (Macrophages)
2. IL-2 (T<sub>H1</sub>)
3. IL-4, 5, 6, 10 (T<sub>H2</sub>)
4. Tumor necrosis factor
5. Interferon
  - ☒ INF-α (WBC): used in HBV, HCV, congenital dyserythropoietic anemia
  - ☒ INF-β (Fibroblasts): used in multiple sclerosis
  - ☒ INF-γ (T<sub>H1</sub>): used in chronic granulomatous disease (CGD)

## Immune Response

T-cell is the orchestrator

1. Antigen processing & presentation on the surface of APC (in association with MHC II)
2. Ag recognition by T<sub>H</sub> cells through TCR-CD<sub>3</sub> complex
3. Activation of T<sub>H</sub> cells → Release of cytokines → ↑↑ B-cells, macrophages, Tc, NK
4. Tc recognizes antigen on target cells e.g., viral-infected cells (in association with MHC I)
5. B-cells → Plasma cells → Antibodies (IgM then IgG)

T Lymphocytes (CMF)	B Lymphocytes (CMF)
Intracellular bacteria (TB, Leprosy, Listeria)	Bacterial infection (Staph, Strept, Pneumo, Hib...)
Viral infection (after cell infection)	Viral infection (before attachment)
Fungal (Candida) & Protozoal infection	Barriers along mucosal membranes (IgA)
Tumors, Graft rejection, type IV hypersensitivity	Type I, II, III hypersensitivity

## Assessment of Immune Competence

### A) Assessment of T-cells

#### 1. T-cell number

- ☒ Absolute lymphocyte count
- ☒ Total T-cells (CD3)
- ☒ T-cell subpopulation (CD4, CD8)
- ☒ CD4/CD8 ratio

#### 2. T-cell function

- ☒ Delayed hypersensitivity skin tests
  - Tuberculin test
  - Candida test
- ☒ Lymphocyte proliferation
  - Mitogen stimulation [Phytohemagglutinin (PHA)]
  - Allogenic stimulation [Non related donor cells]
  - Antigen stimulation [Addition of specific antigen]
- ☒ Cytokine assay
- ☒ Cytotoxicity assay [Tc + target cells = Target cell destruction]

#### 3. CXR (Thymic shadow)

### B) Assessment of B-cells

#### 1. B-cell number

- ☒ Total B-cells (CD19)
- ☒ Serum immunoglobulins (IgG, IgM, IgA)

#### 2. B-cell function

- ☒ Antibody synthesis
  - Naturally-occurring antibodies (Anti-A, Anti-B)
  - Acquired antibodies (after immunization with tetanus or diphtheria toxoids)
- ☒ Lymphocyte proliferation
  - Co-culture of T-cells + B-cells + Pokeweed (mitogen) → Antibody synthesis

#### 4. LN biopsy: absent follicles

### C) Assessment of Phagocytic Function

1. ANC ( $N > 1.500 / \text{mm}^3$ )
2. Chemotaxis
3. ingestion: Direct visualization of ingested particles
4. Rebuck skin window test (In vivo test)
5. Nitroblue tetrazolium test (NBT): assessment of ingestion & intracellular killing
6. Neutrophil respiratory burst assay

### D) Assessment of Complement

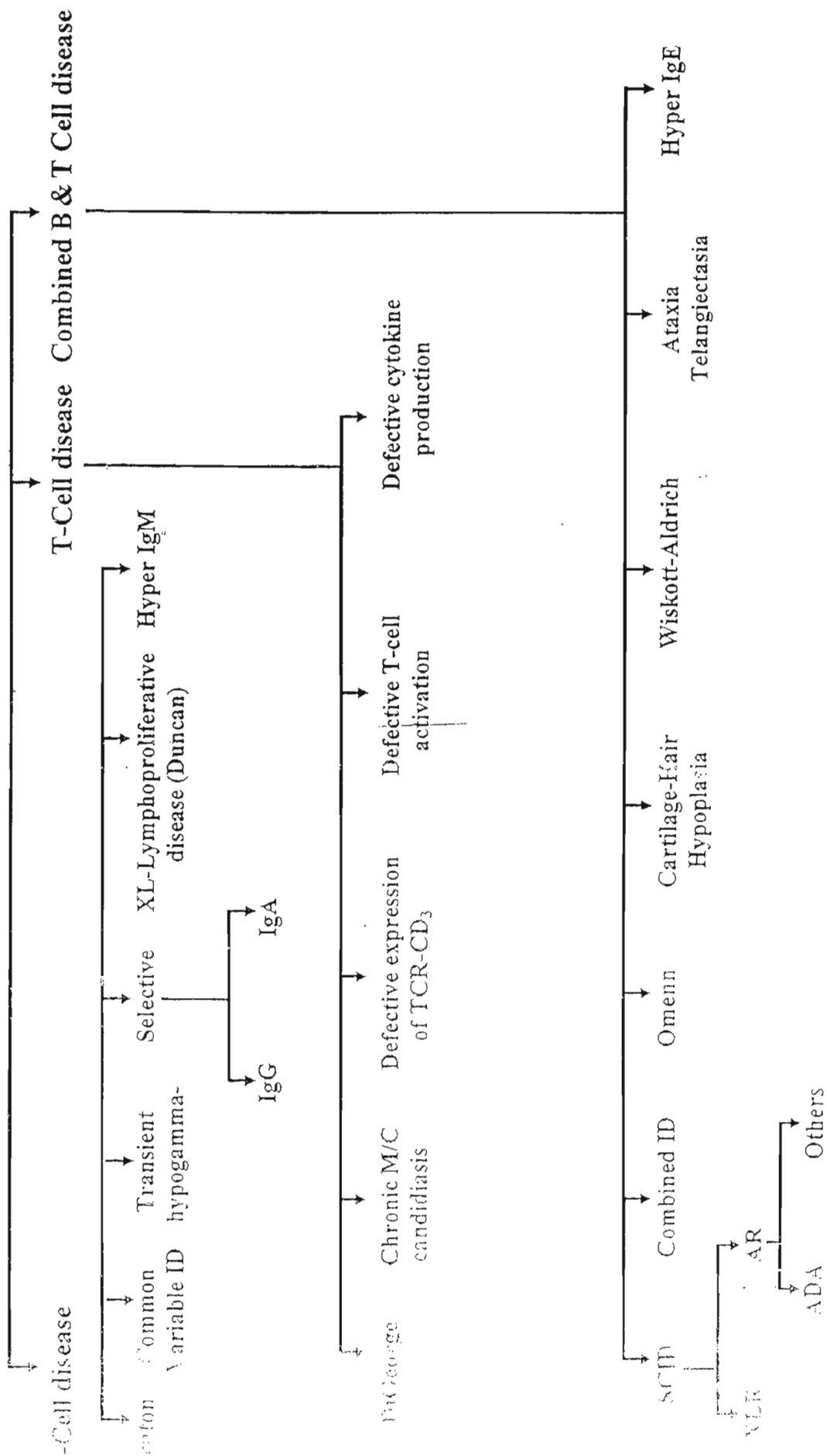
1. Specific factor assay (C3, C4...)
2. Hemolytic activity of the complement ( $\text{CH}_{50}$ )

### E) Others

1. CBC
2. Prenatal diagnosis: Fetal blood investigations



## Primary Immunodeficiency



# Immunodeficiency

## Suspicion of Immunodeficiency

1. Chronic
2. Recurrent
3. Resistant
4. Unusual (site, organism & severity)

Infection

### Opportunistic Organisms

- Pneumocystis carinii
- Toxoplasma
- Candida
- CMV, VZV
- Mycobacteria

B-cell	T-cell	Phagocyte	Complement
Sino-pulmonary Otitis media (Staph, Strep, Pneumo, Hib...)	FTT Viral infections Chronic diarrhea Candida > 6 months GVHD	Deep abscesses Ano-rectal infections	Meningitis Arthritis Angioneurotic edema

## Management of Immunodeficiency

1. Avoid live vaccines
2. Avoid blood transfusion (use irradiated blood, why?)
3. Personal hygiene
4. Prophylactic & therapeutic antibiotics
5. IVIG for hypo- or agammaglobulinemia (400 mg/Kg at monthly intervals), Complications?
6. HSCT, Complications?

IVIG is contraindicated  
in selective IgA deficiency

## Secondary Immunodeficiency

### A) Nutritional

1. Protein energy malnutrition (CMI\*)
2. Copper, Zinc, Iron & Ca deficiency (CMI)
3. Biotin deficiency (candidiasis)

### B) Loss of immunogenic materials

1. Nephrotic syndrome
2. Protein-losing enteropathy
3. Lymphangiectasia (congenital or acquired)

### C) Infection

1. HIV
2. EBV
3. Congenital infection

### D) Immunosuppression

1. Immunosuppressives
  - Steroids (*mention*)
  - Cyclosporine ( $\downarrow$  IL-2, TNF...)
  - Tacrolimus
  - Antibodies: ATG, ALG, OKT3
2. Cytotoxic drugs (affect DNA synthesis)
  - Azathioprine (6-mercaptopurine = abnormal nucleotide)
  - Cyclophosphamide (Alkylating agent)
  - Leflunomide (Dihydrofolate reductase inhibition)
  - Mycophenolate mofetil
3. Radiation

## Primary B-Cell Diseases

### A) X-Linked Agammaglobulinemia (Bruton Disease)

#### Defect

Failure of differentiation of stem cells to pre-B cells

#### Clinical Picture

- Onset: 6-9 month, why?
- Infections: Recurrent bacterial infection (Sino-pulmonary, OM, GE...)
- Organism: (Staph, Strep, Pneumo, Hib...)
- Lymphoid hypoplasia: No LN, No splenomegaly, No tonsillar enlargement
- ↑↑ Risk of malignancy & autoimmune diseases

#### Treatment

- Antibiotics
- IVIG

### B) Common Variable Immunodeficiency

#### Defect

- Acquired condition (2ry to drugs e.g., phenytoin, penicillamine...)
- Failure of differentiation of B-cells into plasma cells

#### Clinical Picture

- Onset: late childhood...
- Lymphoid tissue: Normal or ↑↑ LN, tonsils & spleen

### C) Transient Hypogammaglobulinemia

Defect Exaggeration of normal Ig deficiency > 6 months of age

Clinical Picture Mild bacterial infection (Sino-pulmonary, OM, GE...)

Investigations Normal B & T-cell number

Treatment Not needed

Normally Ig decline reaching a nadir at 3-4 months

### D) Selective IgA Deficiency

#### Defect

- Congenital defect (AD): Defective synthesis or release of IgA
- Acquired condition (2ry to drugs e.g., phenytoin, penicillamine...)

#### Clinical Picture

- May be asymptomatic
- Recurrent bacterial infection (Respiratory, GIT, Urogenital)
- ↑↑ Risk of malignancy & autoimmune (↑↑ Antigenic exposure)

Surface Immunity

#### Investigations

↓↓ Serum IgA

If blood transfusion is indicated, give washed packed RBC's

#### Treatment

- Antibiotics
- IVIG is contraindicated

### E) Selective IgM Deficiency Severe bacterial infection

### F) Selective IgG subclass Deficiency Asymptomatic or bacterial infection

## G) XL-Lymphoproliferative Disease (Duncan)

EBV is oncogenic

**Defect** Defective immune response to EBV

### Clinical Picture

- Age < 5 yrs
- Severe liver necrosis following EBV infection (Mortality = 80%)
- ↑↑ Risk of malignancy: B-cell lymphoma (25%)

### Investigations

- Negative Anti-VCA & anti-EBNA
- ↓↓ Memory T-cell to EBV

**Prognosis** Poor

## H) Hyper IgM syndrome

**Defect** Defective switch (IgM → IgG)

**Clinical Picture** Bacterial infection with ↑↑ Pneumocystis carinii

**Investigations** ↓↓ ANC, ↑↑ IgM, ↓↓ IgG

## Primary T-Cell Diseases

### A) Thymic Hypoplasia (DiGeorge Syndrome)

#### Defect

- Microdeletion (22q)
- Dysmorphogenesis of the 3<sup>rd</sup> & 4<sup>th</sup> pharyngeal pouches
- Aplasia/hypoplasia of the thymus & parathyroid glands

#### Clinical Picture

- Onset: Neonatal period, why?
- Neonatal hypocalcemia
- Infection: Viral, Candida, Chronic diarrhea, FTT, GVHD, P.carinii, certain bacteria
- Facies: Fish mouth, Flat face, short Filtrum & hypertelorism
- Cardiac: Conotruncal anomalies (interrupted aortic arch, truncus arteriosus)

#### Investigations

- Assessment of T-cell
- Serum Ca level, FISH, Echocardiography

#### Treatment

- Hypocalcemia
- HSCT
- Heart surgery?

#### Causes of microdeletion:

1. Prader-Willi
2. Angelman
3. Williams
4. WAGR
5. Alagille
6. DiGeorge



#### Other 22q deletion \$:

1. Velocardiofacial \$
2. Conotruncal-face \$
3. CATCH 22 \$

### B) Chronic mucocutaneous candidiasis

**Defect** Defective immune response to Candida

#### Clinical Picture

- Onset: Variable
- Chronic mucocutaneous candidiasis
- Endocrinopathy: Hypoparathyroidism, Addison (HAM syndrome)

#### DD of candidiasis & Endocrinopathy:

1. Chronic M/C candidiasis
2. Biotin-dependent multiple carboxylase (acidosis, neuro-)

C) Defective Expression of TCR-CD3

D) Defective T-cell Activation

E) Defective Production of Cytokines

# Combined B & T Cell Diseases

## Defect

- Stem cell lesion
- Features of both B & T cell diseases (CMI & humoral immunity)
- Poor prognosis (Death in infancy without HSCT)

## Types

### **A) Severe Combined ID (SCID)**

The first human gene therapy trial was in ADA deficiency (1990)

## Classification

- XLR-Form
- AR-Form
  - Adenosine Deaminase enzyme deficiency ( $\uparrow\uparrow$  deoxyadenosine in B & T cells)  
Rx: Enzyme therapy, HSCT, Gene therapy
  - Others: Jak 3 deficiency...

## Clinical Picture

- Infections: Recurrent bacterial infection (Sino-pulmonary, OM, GE...)  
Viral, Candida, Chronic diarrhea, FTT, GVHD, P.carinii, certain bacteria
- Skin: eruption, alopecia, seborrhea, laxity
- Skeletal: Short stature, skeletal abnormalities (*especially in ADA  $\downarrow\downarrow$* ) & wasting

## Treatment

- Antibiotics
- HSCT

### **B) Combined ID (AR)**

- Infections: as in SCID but milder
- Longer survival
- T-cell function is low not absent as in SCID

### **C) Omenn Syndrome (AR)**

- Combined immunodeficiency
- HSM & Lymphadenopathy
- Intractable diarrhea
- Exfoliative erythroderma
- Eosinophilia &  $\uparrow\uparrow$  IgE

### **D) Cartilage-Hair Hypoplasia (AR)**

- Combined immunodeficiency
- Cartilage: Short-limb dwarfism
- Hair: light, sparse
- Neutropenia

### **E) Wiskott-Aldrich (XLR)**

- Combined immunodeficiency
- Eczema
- Thrombocytopenia (**tiny** platelets)
- HSM & Lymphadenopathy
- Splenectomy may improve thrombocytopenia



**F) Ataxia-Telangiectasia (AR)**

- Combined immunodeficiency
- Cerebellar Ataxia & nystagmus ( $\approx$  at 2 yrs)
- Telangiectasia ( $\approx$  3-6 yrs): Dilated BV on the conjunctiva, lateral aspect of the nose, ears
- Chromosomal breakage
- $\uparrow\uparrow$  Risk of malignancy (Lymphoma & brain tumors): "100-fold"
- $\downarrow\downarrow$  IgA,  $\downarrow\downarrow$  IgG
- $\uparrow\uparrow$   $\alpha$ -Fetoprotein
- Cause of death: Tumors & bronchiectasis

4

**G) Hyper-IgE Syndrome (AD)**

- Combined immunodeficiency
- Recurrent Staphylococcal infection
  - Pneumonia (pneumatocele)
  - Abscess formation (skin, lung...)
- Eosinophilia &  $\uparrow\uparrow$  IgE (non-protective)
- Depressed neutrophil motility
- Rx: Long-term use of anti-Staph. Antibiotics & Rx of pneumatoceles

**Graft Versus Host Disease**

The most common cause  
of morbidity & mortality  
after allogeneic HSCT

**Definition**

- It is tissue damage caused by engraftment of **immunocompetent** donor's lymphocytes in an **immunocompromised** host with **histocompatibility** difference.
- GVHD usually follows HSCT or simple blood transfusion
- It may be beneficial in cases of graft versus leukemia (GVL)

3

**Clinical Picture**

		Acute GVHD	Chronic GVHD
Onset		7-60 days (< 100 days)	> 100 days
C/P	Skin	Erythematous rash	Sclerodermatous changes
	GIT	Secretory diarrhea	Malabsorption
	Liver	Hepatitis	Cholestasis

**Prevention**

1. Proper matching (Histocompatible donors)
2. Post-transplantation immunosuppressive drugs: Methotrexate, Cyclosporine, Steroids
3. Removal of T-cell from the grafts (monoclonal Ab or physical separation)
4. Use of irradiated blood

**Treatment**

Immunosuppressive drugs: Steroids (methylprednisolone), ATG

**Management of Immunodeficiency**

## Disorders of Phagocytic Functions

1. **Degranulation abnormalities:** Chediak-Higashi Syndrome
2. **Adhesion abnormalities:** LAD
3. **Enhanced Motility:** FMF
4. **Depressed Motility:** Drug-induced (steroids) & Hyper-IgE Syndrome
5. **Defects in Microbicidal Activity:** CGD, ↓↓ MPO, ↓↓ G-6-PD, ↓↓ Glutathione
6. **Impaired Spleen Function:** Congenital absence, removal or functional

### Chediak-Higashi Syndrome

#### Etiology

Genetic disease (AR) characterized by giant granules (Defective Degranulation):

- Neutrophils → Neutropenia + ↓↓ Function (chemotaxis, intracellular killing)
- Platelets → ↓↓ Platelet functions
- Melanocytes → ↓↓ Melanin

**Defective Degranulation**

#### Clinical picture

- Infections: Bacterial & fungal (Staph. aureus is the most common)
- Partial albinism, light skin, silvery hair & photophobia.
- Bleeding
- Neuropathy: motor or sensory
- **Accelerated phase** (Lymphoma-like)
  - Cause: Uncontrolled EBV infection
  - C/P: Fever + Severe neutropenia + Pancytopenia + HSM + LN + ↑↑ Mortality

#### Investigations

- CBC [Platelet ( ), ANC ( ), Large inclusions in all nucleated blood cells]
- Bleeding time
- Platelet function

#### Treatment

- Stable phase: Rx of infection & vitamin C (200 mg/day)
- Accelerated phase: Steroids & HSCT

## Adhesion Molecules

#### Definition

They are groups of molecules involved in the adhesion of:

- a. Cell to cell [ $T_H$ +APC and  $T_c$ +Target cell]
- b. Cell to extracellular environment [Homing & migration of cells]

#### Families

1. Cell adhesion molecules (CAMs): ICAM-1, ICAM-2
2. Integrins:  $\beta_1$ -Integrins &  $\beta_2$ -Integrins
  - $\beta_1$ -Integrins mediate leukocyte interaction with the extra-cellular matrix
  - $\beta_2$ -Integrins (include Mac-1, LFA-1) mediate leukocyte adhesion to the endothelial cells & migration out of the blood into the tissues
3. Selectin:

# Leukocyte Adhesion Deficiency (LAD)

## Etiology

Genetic disease (AR) characterized by deficiency of leukocyte adhesion molecules

## Classification

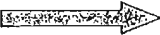
- LAD-1:** Deficiency of  $\beta_2$ -Integrins (Mac-1 & LFA-1) that mediate leukocyte migration
- LAD-2:** Deficiency of Sialyl-Lewis X that mediates leukocyte adherence to endothelial cells

## Clinical picture

- Neonatal period: Delayed separation of umbilical cord, poor wound healing
- Infections:
  - **Bacterial:** Skin (abscess& cellulitis), sinusitis, stomatitis, pharyngitis, OM, pneumonia
  - **Fungal** (Candida & Aspergillus)
- Minimal signs of inflammation
- No pus
- LAD-2: LAD-1 + neurological defects



## Investigations

- CBC: Neutrophilia 
- Phagocytic (Leukocyte) function
  - Chemotaxis (In vitro test)
  - Rebuck skin window test (In vivo test)
  - Nitroblue tetrazolium test (NBT) & Neutrophil respiratory burst assay: Normal
- Monoclonal antibodies directed to leukocyte surface molecules (*Mention...*)
- Biopsy: paucity of inflammatory cells

Basal > 12.000/mm<sup>3</sup>  
Infection > 30.000/mm<sup>3</sup>  
up to > 100.000/mm<sup>3</sup>

## Treatment

- Antibiotics & antifungal
- Prophylactic antibiotics
- Granulocyte transfusion: in severe infection
- HSCT

**Rebuck skin window test**  
Glass cover slip is applied to freshly abraded skin to follow accumulation of WBCs on it.

# Myceloperoxidase Deficiency

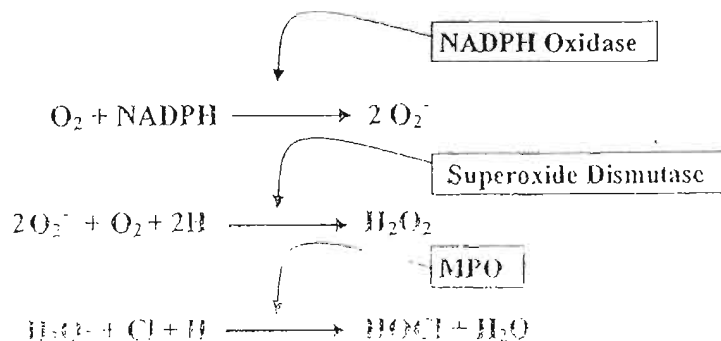
Etiology Deficiency of MPO enzyme

Clinical Picture Usually asymptomatic (Alternative pathway) ??Candida infection

Investigations Enzyme assay

Treatment No specific Rx (Anti-fungal)

Prognosis Excellent





# Chronic Granulomatous Disease (CGD)

## Etiology

- Genetic disease (XLR or AR) characterized by lack of NADPH oxidase enzyme activation
- Failure of intracellular killing of catalase +ve organism (Staph, E.coli, Aspergillus, Candida)
- Granuloma formation (Phagocytes, giant cells & histiocytes)

## Clinical picture

- Infections:
  - Bacterial: Skin (**abscess**, cellulitis & granuloma), **liver abscess**, sinusitis, stomatitis, pharyngitis, OM, **pneumonia**, **osteomyelitis**
  - Fungal (Candida & Aspergillus)
- HSM, LN
- GIT obstruction
- Urethral obstruction



S S S L L L

## Investigations

- Phagocytic (Leukocyte) function
  - Normal chemotaxis
  - Rebuck skin window test (Normal)
  - NBT test (Defective intracellular killing)
  - Neutrophil respiratory burst assay
- Endoscopy, bone X ray, bone scan
- Biopsy: Granuloma (phagocytes, giant cells & histiocytes)

## Treatment

- Prophylactic antibiotics (SMZ-TMP)
- Antibiotics according to culture
- Granulocyte transfusion: in severe infection
- $\gamma$ -Interferon
- HSCT

# Disorders of the Complement System

## Primary Disorders of the Complement System

### Definition

Genetic diseases (AR) characterized by deficiency of one of the factors of the complement system or regulatory mechanisms

### Clinical picture

#### A) Deficiency of complement factors (C1, 2, 3, 4...)

They are characterized by:

- Infections
  - Type: Meningitis, arthritis, pneumonia, abscess, osteomyelitis...
  - Organism: usually caused by Pneumococci, Meningococci, H. influenzae...??
- Autoimmune diseases (Lack of immune complex removal)

#### B) Deficiency of complement regulatory proteins (C1 inhibitor, factor H...)

☒ Deficiency of C1-inhibitor (Hereditary angioneurotic edema)

- AD disease
- Uncontrolled complement activation
- Edema of the affected part, abdominal cramps, diarrhea (intestinal wall edema), laryngeal edema (may be fatal)
- Precipitating factors: Stress, exercise, menses, trauma
- Diagnosis: ↓↓ C4, normal C3, ↓↓ C1-INH
- Management: Avoid...

Infusion of C1-INH (adrenaline, steroids & antihistaminic have No effect)

☒ Deficiency of decay-accelerating factor "DAF" (PNH)

### Investigations Assessment of Complement

### Treatment

- Prophylactic antibiotics & immunization (capsulated bacteria)
- Antibiotics according to culture

## Secondary Disorders of the Complement System

### Pathology

1. ↓↓ Synthesis: PEM, anorexia nervosa, Liver cell failure & preterm infants
2. Complement loss: Nephrotic syndrome (↓↓ Factor B)
3. Consumption
  - Immune diseases. APSGN, MPGN, SLE
  - Shock
  - Burn (↑↑ complement activation)
  - Bacterial endocarditis
  - PNH
  - ECMO & Cardiopulmonary bypass
4. Sickle cell anemia, Splenectomy & Thalassemia major (Defect in complement function)
5. SCID (Due to ↓↓ IgG, how?)

**Nephritic factor (NeF)**  
IgG that promotes complement activation (↓↓ C<sub>3</sub>)

# Hematopoietic Stem Cell Transplantation

## Definition

It is infusion of stem cells into a recipient

## Types

- A) Autologous transplantation (from the same individual)
- B) Allogeneic transplantation (from other compatible individuals)
  - 1. Bone marrow
  - 2. Umbilical cord blood
  - 3. Peripheral blood stem cells

## Indications

- ALL & AML
- Hodgkin & non-Hodgkin lymphoma
- Thalassemia & Sickle cell anemia
- Neuroblastoma & Wilms
- Aplastic anemia
- Fanconi anemia & Dyskeratosis congenita
- Diamond-Blackfan
- PNH
- Osteopetrosis
- Congenital platelet dysfunction
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Omenn syndrome
- Leukocyte adhesion deficiency (LAD)
- Chronic granulomatous disease (CGD)
- Chediak-Higashi disease
- Hyper IgM syndrome
- Kostmann syndrome
- MPS
- Adrenoleukodystrophy

## Preparation

### ☒ Rationale

- a. Ablation of the patient's BM (either normal or abnormal)
- b. Immunosuppression to allow engraftment (prevention of rejection)
- c. Tumor therapy (in cases of malignancy)

### ☒ Method

- a. High-dose chemotherapy [Cyclophosphamide, Busulfan, Cytarabine...]
- b. ± Irradiation

## Post-transplantation (To prevent rejection & GVHD)

Immunosuppressive drugs: Steroids (methylprednisolone), Cyclosporine, Methotrexate

## Evidence of Engraftment

- BM cellularity
- Improved parameters (e.g., immunologic parameters in SCID...)
- Genetic study

SMZ-TMP: for pneumocystis carinii

## Complications

1. Opportunistic infections: prophylactic & therapeutic antimicrobial
2. GVHD (*see immunology*)
3. Graft rejection & graft failure
4. Malignancy
5. HUS, TTP
6. Neurological manifestations due to cranial irradiation or drugs (cyclosporine)
7. Cataract
8. Growth retardation due to irradiation (hypopituitarism), drugs (steroids)
9. Hypothyroidism (primary or secondary)
10. Hypogonadism (primary)

Outcome Depends on etiology & frequency of previous transfusions (10-80%)

# Introduction

## Important Remarks

- ☑ **Incubation period:** Time which lapses between infection & 1<sup>st</sup> clinical manifestation
- ☑ **Prodromal stage:** Clinical manifestations before appearance of the characteristic lesion or rash
- ☑ **Infectivity period:** The period during which the patient can transmit the disease (Measures as isolation are required during this period)
- ☑ **Modes of transmission include:**
  - Droplet infection: e.g., measles, rubella, roseola, chickenpox, diphtheria...
  - Ingestion infection e.g., typhoid fever, poliomyelitis...
  - Contact e.g., tetanus...
  - Arthropod-borne e.g., West Nile fever virus...
  - Congenital e.g., TORCH...
  - Injection e.g., HBV...

## Complications of Infections

- a. **Infectious complications**
  - Measles: May be complicated by otitis media & bronchitis
  - Mumps: May be complicated by meningoencephalitis
- b. **Immunologic complications**
  - Scarlet fever (Streptococci): May be complicated by rheumatic fever or GN
- c. **Mechanical complications**
  - Diphtheria: May be complicated by stridor (Laryngeal membrane)
- d. **Toxic complications**
  - Diphtheria: May be complicated by toxic myocarditis
  - Shigella : Seizures

## General Lines of Diagnosis

1. Clinical diagnosis
2. Serology: Detection of antibodies (IgM)
3. Detection of the organism
  - Direct microscopy
  - Culture
  - PCR (Polymerase chain reaction)

## Prevention

1. General measures: Avoid contact, sanitation, health education, proper nutrition...
2. Specific: vaccine, immune globulins...

## General Lines of Treatment

1. General care
  - Rest
  - light diet (with adequate fluid intake)
2. Symptomatic e.g.,
  - Fever: Antipyretics
3. Specific therapy, e.g., Antibiotics
4. Treatment of complications

# Skin Rashes

## Skin Lesions

- ☒ Macules: Discolored flat spots (Not felt) that blanch on pressure
- ☒ Papules: Solid raised elevations
- ☒ Vesicles: Raised lesions containing clear fluid (< 0.5 cm in diameter)
- ☒ Pustules: Raised lesions containing pus
- ☒ Bullae: Raised lesions containing clear fluid (> 0.5 cm in diameter)
- ☒ Wheals: Well-defined evanescent edematous erythematous itchy lesion
- ☒ Desquamation: Dry flaky loss of surface epidermis

## Maculopapular Rash

### Etiology

#### A) Infections

a. Common infections (Rash is essential for diagnosis)

- Measles
- Rubella
- Roseola infantum
- Scarlet fever

b. Other infections (Rash may be present)

- Typhoid fever
- Infectious mononucleosis
- Enteroviral infections: Coxsackie, Echoviruses...



#### B) Collagen-Vascular Diseases (= Connective tissue diseases or rheumatic diseases)

- a. Systemic lupus erythematosus
- b. Juvenile rheumatoid arthritis (Systemic-onset type)
- c. Dermatomyositis
- d. Henoch-Schonlein purpura

#### C) Skin & allergic diseases

- a. Sweat rash
- b. Drug rash
- c. Urticaria

## Vesicular Rash

### Etiology

#### A) Infections

- a. Chickenpox
- b. Herpes zoster
- c. Herpes simplex

#### B) Skin & allergic diseases

- a. Impetigo contagiosa
- b. Papular urticaria



**Complications** [Common in malnourished & immunocompromised children]**☒ Respiratory**

- Otitis media (*Most common*), laryngitis, laryngotracheobronchitis
- Bronchitis, bronchopneumonia

**☒ Neurological**

- Encephalomyelitis
- Subacute sclerosing panencephalitis (Rare but serious)
  - Definition: Persistent infection with an altered measles virus (in the CNS)
  - Onset of presentation: 7-10 yrs after primary measles infection
  - Clinical manifestations: Personality changes, dementia, seizures..

**☒ GIT: Oral ulcers, gastroenteritis, appendicitis, Kwashiorkor****☒ Others: Optic neuritis, Corneal ulcers****Investigations** (= Clinical diagnosis)

- Measles IgM antibodies
- Viral isolation

**Prevention**

1. Active immunization: Measles & MMR
  - Measles vaccine (was given at 9 ms of age) is now replaced by MMR at 12 ms of age
  - Second dose of MMR is given at 18 months (or later)
2. Post-exposure vaccination: Within 72 hrs of exposure
3. Post-exposure passive immunization: Immune globulin (0.25 ml/kg, IM) is indicated for contacts (especially pregnant females, infants < 6 m & immunocompromised persons)

**Treatment**

1. General care: Rest & light diet (with adequate fluid intake)
2. Symptomatic
  - Fever: Antipyretics
  - Coryza: Decongestants
  - Cough: Cough sedatives
  - Conjunctivitis: Antibiotic eye drops
3. Vitamin A therapy (↓↓ Measles morbidity & mortality)
  - Oral: 100,000 IU for children 6 m-12 m & 200,000 IU for older children
  - IM: in patients with PEM
4. Immune globulin: IM, 1-2 ml/kg in patients with encephalitis
5. Treatment of complications: Pneumonia..

**Differential Diagnosis** Maculopapular rash**DD of common Causes** (Test yourself)

	Measles	Rubella	Roscola infantum
Transmission			
Incubation			
Rash type & site			
Fever-rash relationship			
Prevention			
Main Rx			

# Scarlet Fever

## Etiology

- Erythrogenic toxin produced by group A- $\beta$ -hemolytic streptococci
- Age incidence: 2-10 yrs (more common in spring & winter)

## Mode of Transmission

- Droplet infection

## Incubation Period

- 2-5 days

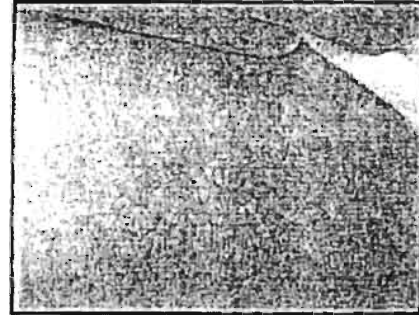
## Clinical Picture

### A) Prodromal stage (2 days)

- FHAM (High fever)
- Sore throat, vomiting & abdominal pain

### B) Exanthem (= Skin Rash)

- Maculopapular (Erythematous = Bright red)
  - Red punctate (blanches on pressure)
  - Finely papular (Sandpaper appearance)
- Appears on D2
- Site of onset: Base of the neck, axilla & groin
- Spread to the whole body
  - Face: Circum-oral pallor is characteristic
  - Cubital fossa: Areas of hyperpigmentation (Pastia lines)
- 1 day to become generalized
- 3-7 days to fade (in the same sequence) by branny desquamation
- Fever-Rash relationship
  - Rash appears on the 2<sup>nd</sup> day of fever
  - The fever rises suddenly as the rash appears



### C) Enanthem (= Mucous membrane Rash)

- Pharynx, Palate & Tonsils: Redness & edema
- Tongue
  - Early (White strawberry): Red edematous papillae emerging through a white coat
  - Late (Red strawberry): The tongue appears red after peeling of the white coat



White strawberry tongue



Red strawberry tongue

**Investigations** (Clinical Diagnosis)A) Evidence of recent Streptococcal infection (*Revise rheumatic fever for details*)

B) CBC: Leukocytosis with predominant PNLs, bandemia &amp; shift to the left

**Complications****☒ Spread of infection:**

- Otitis media, mastoiditis, lateral sinus thrombosis, sinusitis
- Bronchopneumonia
- Osteomyelitis & septicemia

**☒ Late: (Immune-mediated)**

- Rheumatic fever
- Poststreptococcal GN
- Erythema nodosum

**Prevention**

Good housing &amp; adequate ventilation

**Treatment**

1. General Care: Rest & light diet (with adequate fluid intake)
2. Symptomatic
  - Fever: Antipyretics
  - Headache: Analgesics
3. Specific treatment
  - Oral Penicillin V: for full 10 days (Even with early improvement)
  - IM Benzathine penicillin: 600,000-1,200,000 IU (Sensitivity skin test)
  - Oral erythromycin: in patients allergic to penicillin
4. Treatment of complications: F/U is essential to diagnose late complications

**Other Causes of Maculopapular rash****Drug Rash**

- History of drug intake especially penicillins & antipyretics
- Disappear after discontinuation of the offending drug

**Sweat Rash**

- Etiology: Mechanical obstruction of the sweat ducts
- Predisposing factors: Common in infants in hot weather
- Nature of rash: Fine papular with intense erythema, mainly on the neck & trunk
- Rx: Control of environmental temperature, removal of excess clothes & cool baths

**Urticarial Rash**

- Etiology: Allergic reaction to insect bites, drugs, certain foods...
- Nature of rash: Wheals (Well-defined raised erythematous itchy skin lesions)
- Rx: Adrenaline, steroids, antihistaminics

**Typhoid Fever****Enteroviral Infections**



# Chickenpox (Varicella)

## Etiology

- Varicella-Zoster virus
- Highly infectious
- Age incidence: Any age including neonates (Peak = 2-10 yrs)

## Mode of Transmission

- Droplet infection
- Contact with vesicle fluid (Dry scales are not infective)

## Infectivity Period

- 1 day before & 7 days after the onset of the rash

## Incubation Period

- 2-3 weeks

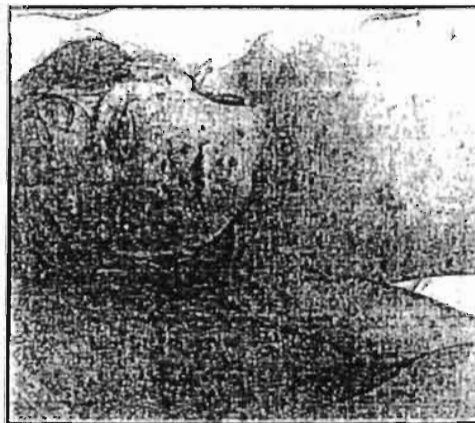
## Clinical Picture

### A) Prodromal stage (1-2 days)

- FHAM
- Mild to moderate

### B) Rash

- Appears on D2
- Site of onset: Trunk (& head)
- Spread to the face, scalp & extremities (Proximal parts)
- Papulo-vesicular rash
  - Distribution: Centripetal
  - Pleomorphic: Successive crops "Different morphology; papules, vesicles & crusts"
  - Pruritis
- All rash duration is 7 days [Papules of the 1<sup>st</sup> crop to the crusts of the last crop]
- No scars except if secondarily infected



## Complications (Commonly in immunocompromised patients e.g., with steroid therapy...)

- ⊗ Secondary bacterial infection
- ⊗ CNS: Encephalitis, myelitis, polyradiculitis, ataxia

## Prevention

1. Active immunization: Varicella vaccine (Live-attenuated) given to children  $\geq$  12 months
2. Post-exposure vaccination: Within 72 hrs of exposure
3. Post-exposure passive immunization [Varicella-Zoster immune globulin (VZIG)]: indicated in immunocompromised patients & susceptible pregnant females

## Treatment

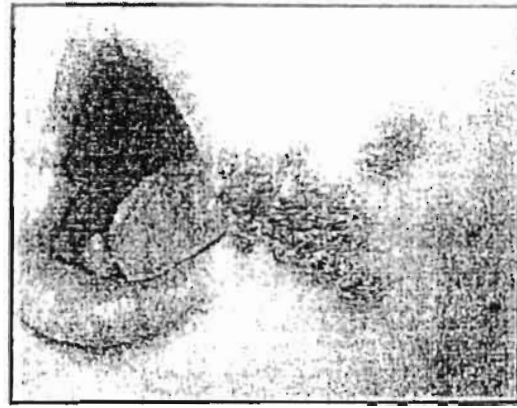
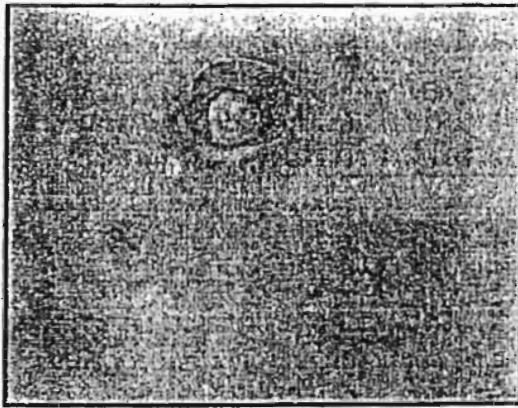
1. General care: Rest & light diet (with adequate fluid intake)
2. Symptomatic
  - Fever: Antipyretics (Not aspirin, why?) →
  - Pruritis: Antihistaminics
3. Specific treatment
  - Antiviral (IV acyclovir): In immunocompromised patients
4. Treatment of complications: Antibiotics: 2ry bacterial infection

**NB: Reye Syndrome:** Interaction of viral infection & Salicylates use in a genetically predisposed individual

## Other Causes of Vesicular rash

### Impetigo Contagiosa

- Etiology: Staphylococci & Streptococci
- Site: Exposed areas as the face, neck & limbs (but any site can be affected)
- Predisposing factors: Children especially in hot weather
- Nature of rash: Erythematous macules → Vesicles & pustules → Crusts
- Mucous membranes are spared
- Rx: Local fucidinic acid (Systemic flucloxacillin may be used in severe cases)



Impetigo contagiosa (Note erythematous macules & yellowish crusts)

### Papular Urticaria

- Etiology: Delayed hypersensitivity reaction to insect bites (e.g., Fleas, mites...)
- Site: Extensor surface of extremities
- Nature of rash: Papules that may vesiculate



Urticaria



Papular urticaria

# Mumps

## (Epidemic Parotitis)

### Etiology

- Mumps virus (Myxovirus parotitis)
- Age incidence = 5-15 yrs (more common in spring & winter)

### Mode of Transmission

- Droplet infection (Saliva)
- Contact with virus-containing secretions of an infected person

### Infectivity Period

- 7 days before & 7 days after the appearance of salivary gland swelling

### Incubation Period

- 2-3 weeks

### Clinical Picture

#### A) Prodromal stage (1-2 days)

- FHAM
- Mild (may be absent)

#### B) Salivary gland involvement

##### a. Parotid gland

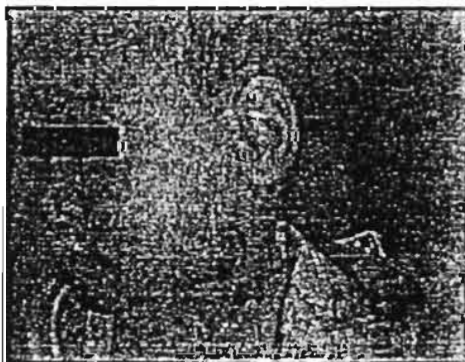
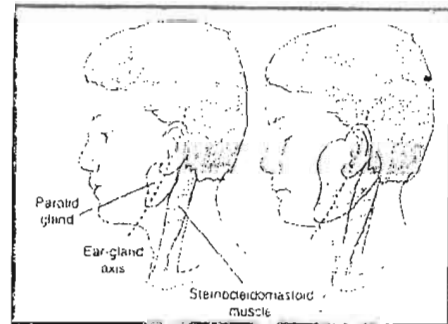
- Incidence: Commonest gland to be involved
- Clinical Picture
  - Pain: aggravated by chewing movements & sour drinks (e.g., lemon juice)
  - Stensen duct opening: Hyperemia
  - Swelling:
    - Fills the space behind the mandible
    - Angle of the mandible is not visible
    - Raises the ear lobule & extends anterior to it
    - Tender
    - Usually bilateral (Unilateral in 25% However, one may precede the other)
    - Reaches maximum size in 1-3 days & subsides within 7 days

##### b. Submandibular

- Incidence: 10-15 %
- May be the only manifestation

##### c. Sublingual

- Incidence: Least common
- Extremely painful



Anterior

Posterior



## Complications

### 1. Meningoencephalomyelitis

#### ☒ Incidence

- Commonest complication in children
- ♂:♀ = 3:1

#### ☒ C/P

- Onset: It usually occurs 5 days after parotitis but it may precedes or accompanies
- CNS affection may be isolated (Without salivary gland involvement)
- C/P: Viral encephalitis,...

#### ☒ Investigations

- CSF: ↑↑ Cells (Lymphocytes) + ↑↑ Proteins + Normal glucose

#### ☒ Treatment

- Supportive (Seizures + ↓↓ ICT)

### 2. Epididymoorchitis

#### ☒ Incidence

- It occurs in 15-35% of adolescent & adults ♂
- Extremely rare in pre-puerperal children

#### ☒ C/P

- Onset: It usually occurs 10 days after parotitis but it may precedes or accompanies
- It may be isolated (Without salivary gland involvement)
- C/P: Swelling, tenderness, redness, lower abdominal pain, fever & chills
- Testicular atrophy may occur (in 30-40%) but infertility is rare

### 3. Pancreatitis

#### ☒ Incidence

- Mild or subclinical pancreatitis are common (Severe pancreatitis is rare)

#### ☒ C/P

- Onset: It usually occurs 3-10 days after parotitis
- It may be isolated (Without salivary gland involvement)
- C/P: Epigastric pain, tenderness, vomiting, fever
- Elevated serum amylase is diagnostic

### 4. Oophoritis

- It occurs in 7% of adolescent & adults ♀
- May cause severe pain & when on the right side may be confused with appendicitis

### 5. Deafness (Auditory neuritis)

- Rare but serious (Hearing loss may be permanent)
- Usually unilateral

### 6. Myocarditis

- C/P: Heart failure (3 T) + ECG changes
- Self-limited

### 7. Arthritis

- C/P: Rare, affecting small & large joints (migratory)
- Mild & self-limited

### 8. Thyroiditis

### 9. Thrombocytopenia

### 10. Ocular: Optic neuritis, scleritis, central vein thrombosis

# Tetanus

## (Lockjaw)

### Etiology

- *Clostridium tetani* (Gram +Ve Anaerobic, Spore-forming bacilli)
- *Cl. tetani* secretes a potent neurotoxin "Tetanospasmin" which ↑↑ neuronal excitability

### Mode of Transmission (Contact with tetanus Spores)

- Wound contamination (in polluted places)
- Neonatal infection: Umbilical stump (Tetanus neonatorum)
- Surgical & puerperal infection

### Incubation Period

- 2-14 days

### Clinical Picture

- Trismus (Lockjaw): Occurs in > 50 % of cases
- Inability to suck, dysphagia
- Risus sardonicus: Spasm of the angle of the mouth
- Neck stiffness
- Head retraction
- Opisthotonos position
- Convulsions
- Cyanosis
- Normal consciousness
- Normal sensory function
- Autonomic dysfunction: heart rate, BP, temperature...
- Any minor stimulus (Sound, light or touch) may trigger a tetanic spasm



### Complications

#### A) Respiratory complications

1. Pneumonia: Aspiration
2. Emphysema & Pneumothorax
3. Collapse

#### B) Other complications

1. Convulsions: Aspiration, injury
2. Vertebral fractures
3. Autonomic complications: Arrhythmias, labile BP & temperature regulation

### Investigations (Clinical Diagnosis)

Isolation of the organism: Gram +Ve bacilli with drum-stick appearance (In 1/3 of cases)

### Differential Diagnosis

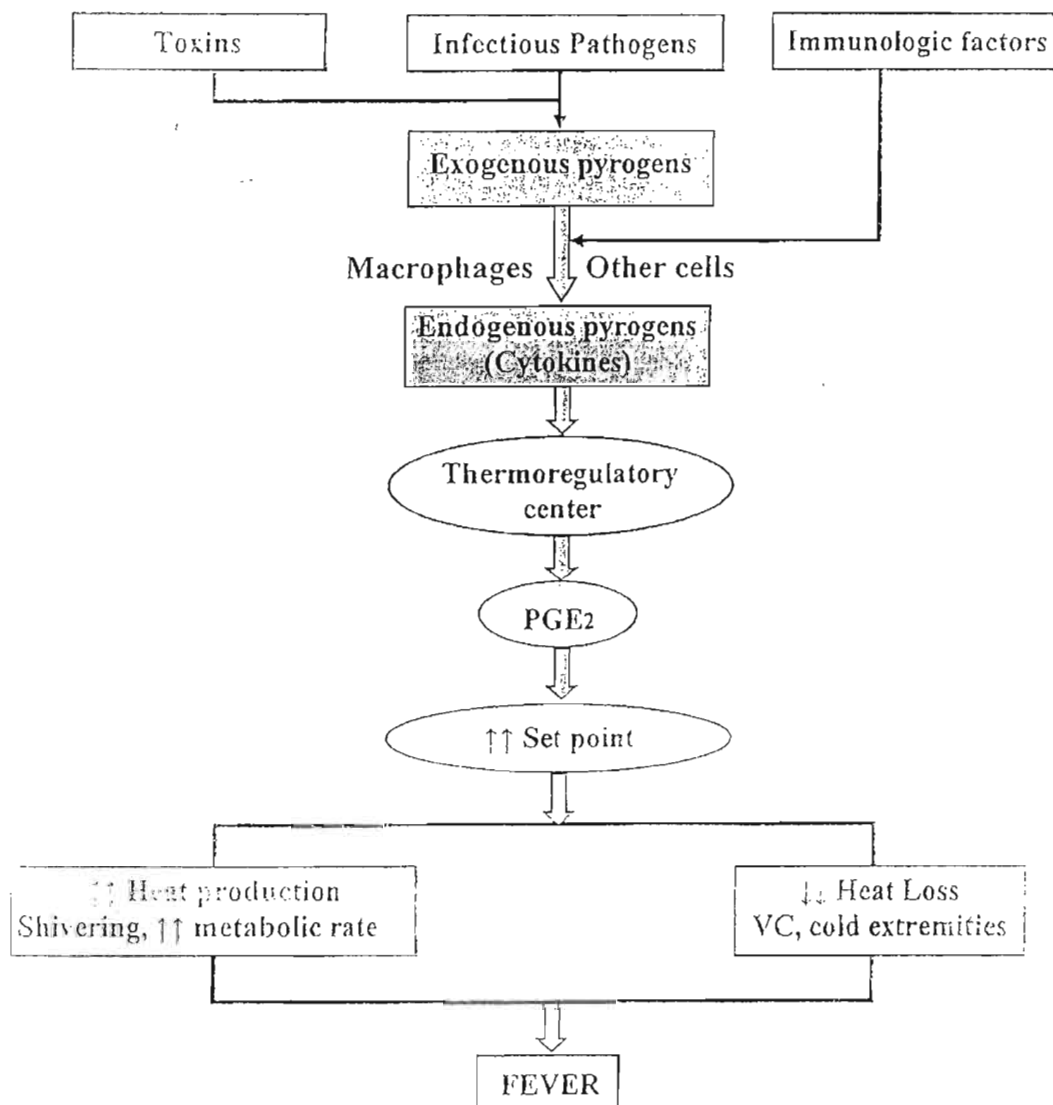
1. Other causes of trismus. e.g.:
  - Peritonsillar abscess
  - Retropharyngeal abscess
  - Dental abscess
2. Meningitis
3. Epilepsy
4. Tetany: Carpopedal spasm
5. Rabies: Hydrophobia
6. Strychnine

# Fever (Pyrexia)

## Definition

- Elevation of body temperature
  - Oral measurement  $> 37.2^{\circ}\text{C}$
  - Rectal measurement  $> 37.7^{\circ}\text{C}$
- Elevation of body temperature due to high environmental temperature beyond the capacity of the heat regulating center (hyperthermia) is not true fever
- Fever is a symptom (Not a disease)

## Pathogenesis



## Benefits of Fever

- ↑↑ Leukocyte migration & phagocytosis
- Decreases microbial cell division

## Purpuric Rash (Fever with purpura)

### Etiology -

#### A) Bacterial infections (20 % of cases)

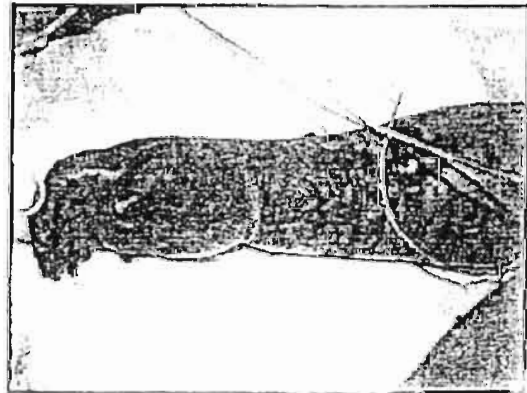
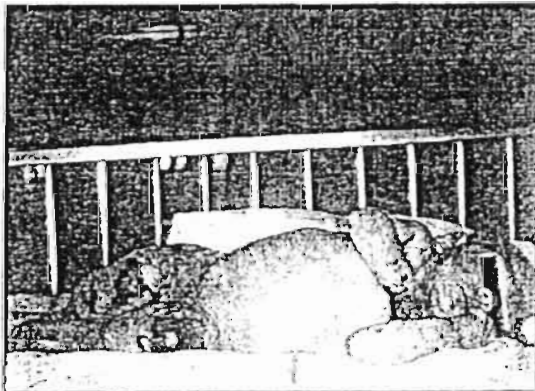
- Meningococci
- Staphylococci
- Streptococci
- Hemophilus influenza type b
- Listeria

#### B) Viral infections (80 % of cases)

- Enteroviruses (especially Echovirus type 9)
- CMV
- Hemorrhagic fevers (Black measles & Dengue fever)

### Management

- Hospitalization
- Investigations: CBC, CRP, ESR, Cultures (Blood & CSF)
- Urgent parenteral antibiotics for bacterial causes



**Meningococemia**

### Adverse Effects of Fever

- Weakness & fatigue
- Anorexia
- Destruction of body proteins & fats
- Febrile convulsions (In genetically predisposed patients)

### Grades of Fever (Rectal)

Grade	Temperature
Mild fever	37.8-38.4°C
Moderate fever	38.5-39.4°C
High fever	39.5-41°C
Hyperpyrexia	> 41°C

### Hyperthermia

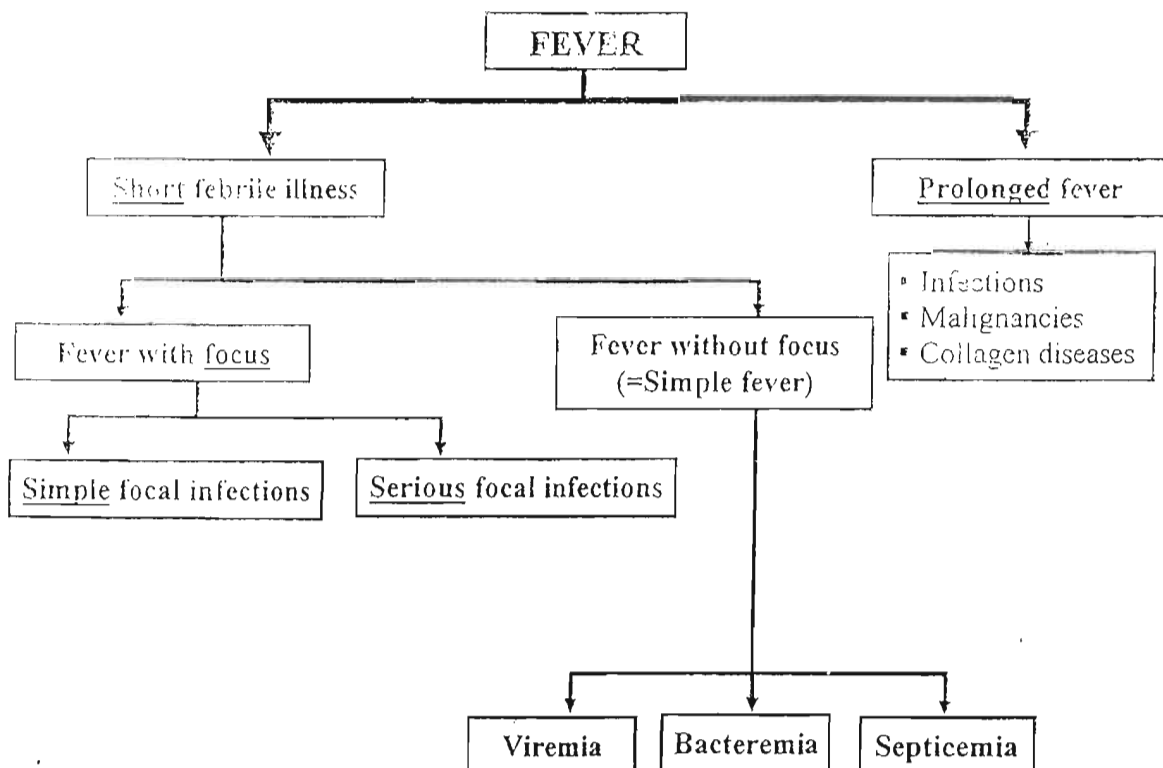
- ☒ **Definition:** Elevation of body temperature due to ↑↑ environmental temperature
- ☒ **Etiology:**
  - Heat stroke
  - Hot weather & inadequate breast milk in neonates (dehydration fever)
  - ↑↑ Incubator temperature
- ☒ **Clinical Picture:**
  - The patient feels hot
  - Extremities are hot
- ☒ **Treatment:**
  - Oral or IVF
  - ↓↓ Environmental temperature

#### **Remember**

##### True fever:

- The patient feels cold
- Extremities are cold (VC)

### Etiology of Fever





## Short Febrile Illness

### A) Fever with focus (Focal infections)

- a. Simple focal infections e.g., Nasopharyngitis, tonsillitis, sinusitis, otitis media, bronchitis, GE, cystitis, abscess, cellulitis...
- b. Serious focal infections e.g., Pneumonia, peritonitis, pyelonephritis, arthritis, osteomyelitis, meningitis...

### Clinical exclusion of serious focal infections

Serious focal infections	Features
Pneumonia	Respiratory distress, chest findings (bronchial breathing, crepitations)
Peritonitis	Tenderness, rebound tenderness, rigidity, associated ileus
Pyelonephritis	Loin pain, abdominal pain with dysuria and frequency
Arthritis, Osteomyelitis	Joint tenderness & painful limitation of movement ± redness, hotness & swelling
Meningitis	Neck rigidity, convulsions, lethargy or unconsciousness

### Important Remarks

1. Otitis Media is very common in infants & children & should be routinely excluded
2. Vomiting is **not** a localizing manifestation (GIT, Renal, Respiratory...)
3. Initially the focus may not be evident. **Re-examination** after 24-48 hrs is important
4. Urinary symptoms may be difficult to elicit in infants and young children

### B) Fever without focus (=Simple fever)

- a. Viremia
- b. Bacteremia
- c. Septicemia

## Fever without Focus (Simple Fever-Nonspecific fever)

### Definition

- Short febrile illness without a focus
- The most important step is to differentiate between viral (Viremia) from bacterial infections (Bacteremia & Septicemia)
- Viral infections are more common, bacterial infections are more serious
- Differentiation is mostly related to the general condition (more than the degree of fever)
- Clinical differentiation can be difficult in neonates and young infant
- Laboratory findings suggesting bacterial infection include:
  - Leucocytosis or leucopenia
  - Leukocytosis with neutrophilia, bandemia (>10%) and shift to the left
  - Significant increase in CRP and ESR
  - Positive culture (takes 2-3 days)
- Viremia without other manifestations may represent the prodroma of one of the viral exanthemata (e.g., Measles, roseola infantum...)

## General Clinical Assessment

- Evaluation of the general condition by the general clinical assessment is very helpful
- It is based on criteria obtained by history or examination

History	Examination
Appetite	Appearance (Healthy or sick)
Activity	Conscious level (Alert, drowsy or comatose)
Reaction to parents (Mood)	Reaction to social stimulation

### Sick child

- Pale
- Toxic
- Lethargic
- Shocked: Cold extremities, poor capillary perfusion, mottling, hypotension

	Viremia	Bacteremia	Septicemia
<b>Fever</b>	Mild to Moderate	High fever	High fever or Hypothermia
<b>General clinical Assessment</b>	Fair general condition	Sick	Seriously ill, organ dysfunction may be present ( <i>see below</i> )
<b>Investigations</b>		Laboratory evidence of bacterial infection ( <i>See above</i> )	<ul style="list-style-type: none"> <li>▪ Laboratory evidence of bacterial infection</li> <li>▪ Obtain cultures as needed</li> <li>▪ Others according to clinical picture (CXR, blood gases, creatinine, CSF...)</li> </ul>
<b>Management</b>	<ul style="list-style-type: none"> <li>▪ Antipyretics               <ul style="list-style-type: none"> <li>- Paracetamol</li> <li>- Ibuprofen</li> </ul> </li> <li>▪ Re-examination:               <ul style="list-style-type: none"> <li>- After 24-48 hrs</li> <li>- May reveal a focus</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ Oral broad-spectrum antibiotic (Amoxicillin)</li> <li>▪ Antipyretics               <ul style="list-style-type: none"> <li>- Paracetamol</li> <li>- Ibuprofen</li> </ul> </li> <li>▪ Re-examination:               <ul style="list-style-type: none"> <li>- After 24-48 hrs</li> <li>- May reveal a focus</li> <li>- Response to Rx</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ Urgent hospitalization</li> <li>▪ Parenteral antibiotics</li> <li>▪ Supportive treatment and antipyretics</li> </ul>

## Septicemia

### Definition

- Severe systemic bacterial infection potentially associated with multiple organ dysfunction.

### Clinical Picture

- Fever: High or hyperpyrexia, sometimes hypothermia (especially neonates)
- General clinical assessment: Sick & seriously ill (*Discuss*)

## Investigations

- CBC
  - TLC  $> 15,000/\text{mm}^3$
  - TLC  $< 5,000/\text{mm}^3$
  - Bandemia  $> 10\%$
  - Shift to the Lt
- CRP:  $\uparrow\uparrow$
- ESR:  $\uparrow\uparrow$
- Blood C&S
- Urine C&S
- Sputum/ Gastric aspirate C&S
- CSF
- CXR, ABG, renal functions, coagulation studies.

## Complications

1. Serious focal infections: osteomyelitis, arthritis, meningitis
2. Septic shock
3. Shock lung (ARDS = Acute respiratory distress syndrome)
4. Toxic encephalopathy
5. Acute renal failure
6. Sclerema
7. DIC
8. Thrombocytopenia
9. Acute hemolytic anemia

## Management

### A) Urgent hospitalization

- ☒ Investigations
- ☒ Immediate treatment (Parenteral antibiotics)
- ☒ Detection & management of possible complications

### B) Urgent investigations

Treatment should be started without delay then modified according to the result of culture

### C) Urgent parenteral antibiotics

- ☒ Route: IV
- ☒ Type: Initial broad spectrum [Ampicillin + Gentamicin]
- ☒ Treatment should be started without delay then modified according to the result of culture

### D) Control of high fever

- ☒ Rectal or IV Paracetamol
- ☒ Other antipyretics as ibuprofen or diclofenac
- ☒ IV Acetylsalicylic acid (Hyperpyrexia): May be given in older children

### E) Feeding

- ☒ IVF
- ☒ Oral: after stabilization

### F) Treatment of complications

- ☒ RD: Oxygen, may be mechanical ventilation
- ☒ Septic shock: Volume expansion, drugs e.g., Dopamine
- ☒ Convulsions, ARF, DIC...

### Important Remarks

- Start with simple investigations
- Proceed according to clinical suspicion and results of previous investigations
- Patients with good general condition and normal initial studies may be managed on OP basis with additional investigations as needed and follow up. Benign viral infection may be the cause
- Those with clinical or laboratory findings suggesting significant illness should be hospitalized

### Treatment

#### A) Supportive Measures

- ☑ Management of febrile child
- ☑ Stop all unnecessary drugs (Drug fever)

#### B) Specific Measures

- ☑ Treatment of the cause
- ☑ Avoid empirical treatment (It may mask the condition & delay the diagnosis)
- ☑ Empirical treatment is indicated in:
  - Septicemia: Antibiotics should be started immediately (Organism can be identified in only 50% of patients)
  - Anti-TB drugs: when TB is highly suspected

### Prognosis

- Unlike in adults, prolonged fever in children is usually benign
- Prognosis is generally good
- In many patients the fever subsides without diagnosis & even before completion of investigations
- The cause of the fever remains unclear in about ¼ of cases

## Management of Febrile child

#### A) General Measures

- ☑ Bed rest
- ☑ Light diet (with adequate fluid intake)
- ☑ Multivitamins: in cases with prolonged dietary restriction
- ☑ IVF: for correction of dehydration & electrolyte disturbances (may be needed)

#### B) Antipyretic Measures

- ☑ Cold fomentation using tap water (↑↑ Heat loss through the skin)
- ☑ Iced water should be avoided, why? (Peripheral VC & ↓↓ heat loss)
- ☑ Antipyretics:
  - Action: Inhibit PG synthesis → Set point returns to normal → Decrease heat production & ↑↑ heat loss (sweating) → Improvement of fever
  - Route: Usually oral or rectal (Parenteral route is available for some antipyretics)
    - Parenteral route (IV) is used in cases of hyperpyrexia (Temperature > 41°C)
    - Parenteral route (IV) is available for paracetamol & acetylsalicylic acid
  - Frequency: Variable (4-8 hrs)
  - Examples

## Prolonged Fever

### Definition

- Fever with duration > 10-14 days
- Less common than short febrile illness but causes greater concern to parents & doctors
- Documentation of fever is important:
  - Parents may misinterpret normal temperature as mild fever
  - The fever may be 2 short febrile illnesses rather than prolonged fever

### Fever of Unknown Origin

- Fever documented by a health care provider with its cause could not be identified after:
  - 3 weeks of evaluation as an outpatient
  - 1 week of evaluation (History, examination & routine investigations) in hospital

### Etiology

#### a. Infections:

- ☒ Bacterial
  - Systemic infections: e.g., Salmonellosis, Brucellosis, Tuberculosis
  - Hidden focal infections: e.g., Pyelonephritis, endocarditis, osteomyelitis, Abdominal abscess (Liver, perinephric, pelvic...)
- ☒ Viral: e.g., CMV, Infectious mononucleosis (EBV), Hepatitis, HIV
- ☒ Parasitic: e.g., Malaria, Leishmaniasis, Toxoplasmosis

#### b. Collagen-Vascular diseases: SLE, JRA, Rheumatic fever

#### c. Malignancy: Leukemia, Lymphoma, Neuroblastoma

#### d. Others: e.g., Inflammatory bowel disease, drug fever

## Management of prolonged fever (= FUO)

### A) Documentation of fever

### B) Meticulous history & careful examination

- May reveal or suggest the cause of fever
- Nonspecific findings denoting significant illness:
  - History: Anorexia & weight loss
  - Examination: Pallor, toxic look, cachexia, LN, HSM

### C) Investigations

- CBC, ESR, CRP (abnormal results may indicate significant illness)
- UA, urine and blood cultures
- Tests for specific infections (Tuberculin, Widal, Brucella, Monospot, ...)
- CXR and abdominal U/S
- ANA, Anti DNA (Collagen-vascular diseases)
- Further investigations: Echocardiography, LN biopsy, BM examination

### D) Hospital management

- Documentation of fever
- Stop all drugs (To exclude drug fever)
- Observation & regular full examination
- Proceed with investigations

# **PEDIATRIC RHEUMATOLOGY**

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# Rheumatic Diseases

## (Collagen vascular diseases)

### Definition

They are heterogeneous group of disorders sharing the certain features:

1. **Etiologically**: Unknown; most probably immune dysregulation (genetic, hormonal & environmental factors may have a role)
2. **Pathologically**: Inflammation (treated with steroids & other immunosuppressives)
3. **Clinically**: Multi-system affection (Fever, joints, cutaneous, serosal, cardiac, renal...)

## Investigations of Rheumatic Diseases

### A) Laboratory

#### ☒ Blood

- **CBC**:
  - Hb (anemia of chronic diseases)
  - WBC (↑↑ in SOJRA, ↓↓ in SLE)
  - PLT (↑↑ in Kawasaki & SOJRA, ↓↓ in SLE)
- **ESR**: usually ↑↑ (Not diagnostic, used for follow-up)
- **CRP**: +ve CRP in SLE usually indicates infection
- **ANA** (anti-nuclear Ab): screening test
  - **Titer**: (Titer > 1/80 is significant)
  - **Pattern**: (*Rim* "specific to SLE", *Homogenous* & *Speckled*)
- **Anti-ds DNA**: specific for SLE
- **ANCA** (Anti-neutrophil cytoplasmic Ab): Wegener granulomatosis & Churge-Strauss \$
- **Anti-centromere Ab**: in scleroderma
- **Antiphospholipid Antibodies** (lupus anticoagulant & anticardiolipin antibody): ↑↑ in antiphospholipid syndrome (1ry or 2ry to underlying disease; SLE, infections...)
- **Rheumatoid factor**: IgM against IgG
- **LE cells**: WBC that had ingested "DNA-Anti-DNA complexes"
- **KFTs, Electrolytes, albumin, total proteins & cholesterol**: Renal affection
- **Liver function tests**: Methotrexate toxicity
- **C<sub>3</sub> & C<sub>4</sub>**: Consumed in immune processes involving Ag-Ab reactions (e.g., SLE...)
- **HLA typing**: (?linkage or due to antigenic similarity with some pathogens)
  - Ankylosing spondylitis: HLA-B27
  - SLE: HLA-B8, DR2, DR3
  - JRA: HLA-DR4

#### Markedly ↑↑ ESR occurs with:

1. Collagen vascular diseases
2. Malignancy
3. TB

#### ☒ Urine

- **Urinalysis**: (hematuria, pyuria & casts)
- **Urinary albumin/creatinine ratio** (Normally < 0.2)
- **Urine culture & sensitivity**

### B) Imaging

- **CXR**: Cardiomegaly, pulmonary congestion & infection
- **Echocardiography**: Coronary dilatation & aneurysm formation in Kawasaki  
Pericardial effusion in SLE & SOJRA  
Ventricular hypertrophy in Takayasu arteritis
- **Doppler**: for detection of thrombotic events in antiphospholipid \$ e.g., DVT...
- **CT & MRI**: ICH (HTN), brain infarction (antiphospholipid \$)
- **Renal ultrasonography**: Size, echogenicity, cortico-medullary differentiation

### C) Invasive:

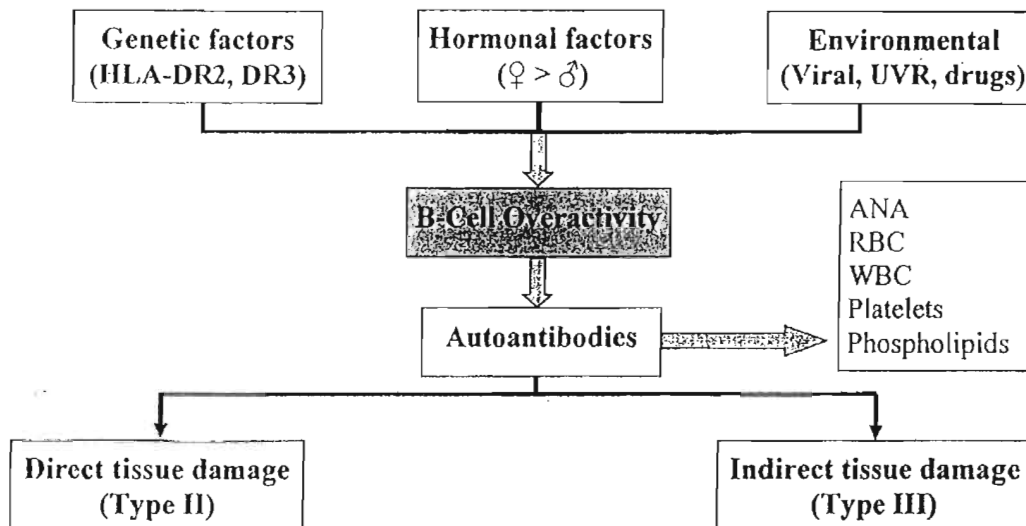
- **Skin biopsy**: in HSP & vasculitis
- **Renal biopsy**: (WHO grades SLE)

# Systemic Lupus Erythematosus

## Definition

It is multisystem disease characterized by widespread organ involvement

## Pathogenesis



## Diagnostic Criteria of SLE

Criterion	Definition
1. Malar rash	Erythematous malar rash sparing the nasolabial folds
2. Discoid rash	Erythematous raised patches (scaly)
3. Photosensitivity	Unusual reaction to sunlight
4. Oral ulcers	Usually painless
5. Arthritis	Non-erosive $\geq 2$ joints
6. Serositis	a. Pleurisy: Typical pleuritic pain or rub b. Pericarditis: Rub, ECG or effusion
7. Renal	a. Proteinuria $> 0.5$ g/day b. Cellular casts (RBC, granular...)
8. Hematological	a. Hemolytic anemia b. Leukopenia ( $< 4,000/\text{mm}^3$ ) c. Lymphopenia ( $< 1,500/\text{mm}^3$ ) d. Thrombocytopenia ( $< 100,000/\text{mm}^3$ )
9. Neurological	a. Seizures: in absence of offending drugs or metabolic derangement b. Psychosis: in absence of offending drugs or metabolic derangement
10. Immunological	a. Anti-DNA antibodies b. Anti-Smith antibodies c. Anti-phospholipid antibodies (Lupus anticoagulant &/or Anticardiolipin) d. False positive tests for syphilis
11. ANA	

## Important Remarks

- ☑ SLE is diagnosed if there are 4 out of the 11 criteria [Serially or simultaneously during any interval of observation]
- ☑ "LE cells" criterion is now deleted
- ☑ Patients suspected to have SLE should receive appropriate Rx even with  $< 4$  criteria



## Clinical Picture

**Onset:** Acute or gradual

**Course:** Remission & exacerbation

**Age:** Usually > 8 yrs

**Sex:** (♀ > ♂)

### **Presenting manifestations**

- Constitutional: FHAM, loss of weight
- Musculoskeletal: Arthralgia, arthritis
- Skin: 4 + vasculitis, alopecia, livedo reticularis
- Renal: GN, NS, HTN
- CVS: Pericarditis
- Neurologic: 2 + stroke, chorea
- Pulmonary: Pleurisy
- Hematologic: Anemia, purpura, leukopenia
- Laboratory: ↑↑ ESR, ANA, ↓↓ C<sub>3</sub> & C<sub>4</sub>

	APSGN	MPGN	SLE
C <sub>3</sub>	↓↓	↓↓	↓↓
C <sub>4</sub>	Normal	↓↓ or normal	↓↓

## Investigations

- **ANA:** Sensitive screening test
- **Anti-dsDNA:** Specific for SLE
- **Anti-histone Ab:** in drug-induced SLE
- **Renal biopsy:** Indicated in any patient with SLE with nephritis

## Treatment

- Rx depends on the affected organs & severity of the disease
- Rx is guided by clinical response & laboratory markers (ESR, ANA, C<sub>3</sub> & C<sub>4</sub>)

1. **Avoid sun exposure & the use of sunscreen**
2. **Topical steroids:** Discoid lupus
3. **NSAIDs:** Arthritis & Arthralgia
4. **Hydroxychloroquine:** Cutaneous aspects of SLE
5. **Anticogulant therapy (Heparin & warfarin):** Thrombosis (APS)
6. **Corticosteroids**

### **Pulses of Methylprednisolone**

1. ↑↑ anti inflammatory ef
2. ↓↓ steroid side effects

- a. **Systemic disease:** 1-2 mg/Kg/day till remission followed by gradual tapering
  - b. **Severe disease:** Pulse methylprednisolone 30mg/Kg/dose for 3 days is given initially
7. **Cytotoxic therapy** (used in severe disease to # progression of renal disease)
    - a. **Cyclophosphamide:** IV (500 mg/m<sup>2</sup>/dose)/ ms [6 doses] followed by IV/3 ms [6 doses]
    - b. **Azathioprine** (2 mg/Kg/day)
    - c. **MMF**
    - d. **MTX**
  8. **Other lines of Rx:** IVIG, Plasmapheresis, Rituximab (Anti-CD 20 monoclonal Ab)
  9. **Autologous HSCT**
  10. **Management of Complications**
    - Renal failure: Dialysis & renal transplantation
    - Seizures: Anticonvulsant
    - HTN: Antihypertensives
    - Infection
    - Stroke

## Prognosis

- Early diagnosis & proper Rx improve the outcome
- Major causes of death: Renal disease, CNS, infection, pulmonary hemorrhage

## GN associated with SLE (Lupus Nephritis)

Renal affection is one of the most common feature of SLE & may be the only manifestation

WHO Class	Description	Pathology		Clinical Picture	Treatment
		I/M	I/F & E/M		
I	No histologic abnormalities			No clinical renal signs	No Rx
II	Mesangial lupus nephritis	Mesangial proliferation Mild = II-A Moderate = II-B	Mesangial deposits	Hematuria (microscopic) Proteinuria (mild) Normal renal function	Prednisone (1-2 mg/Kg/day) tid (till remission) followed by Slow tapering over 4-6 months
III	Focal segmental lupus nephritis	Focal & segmental mesangial proliferation Capillary wall necrosis, sclerosis, crescent formation	Mesangial & subendothelial deposits	Some as Class II Some as Class IV	Some as Class II Some as Class IV
IV	Diffuse proliferative lupus nephritis (wire-loop GN)	All glomeruli show mesangial proliferation Capillary wall necrosis, sclerosis, crescent formation	Mesangial & subendothelial deposits	Hematuria Proteinuria (NS) Renal insufficiency	As class II + Cyclophosphamide IV (500 mg/m <sup>2</sup> /dose) / month [6 doses] followed by IV/ 3 months [6 doses] Azathioprine & MMF may be used
V	Membranous glomerulopathy	Thickening of the GBM (spikes) Mild mesangial proliferation	Subepithelial deposits	Nephrotic \$	Steroids + Chlorambucil

Deposits = Ig & complement, Mesangial proliferation = ↑↑ cells + ↑↑ matrix, MMF = Mycophenolate Mofetil

**Pulses of Methylprednisolone:**  
1. ↑↑ anti inflammatory effect  
2. ↓↓ steroid side effects

**Deterioration of renal function in SLE:**  
1. Active lesion (↑↑ Rx)  
2. Sclerotic lesions  
3. Nephrotoxicity

**Aim of Rx** Induction of clinical & serologic remission

### Activity & Chronicity indexes

Activity lesions		Chronicity lesions	
Glomerular	Tubulointerstitial	Glomerular	Tubulointerstitial
Capillary hypercellularity Fibrinoid necrosis Cellular crescents Leukocyte infiltration	Mononuclear cell infiltration Tubular necrosis	Glomerular sclerosis Fibrous crescents Fibrous adhesions Extramembranous deposits	Interstitial fibrosis Tubular atrophy
Activity lesions are <b>potentially reversible</b> with Rx		Chronicity lesions are <b>irreversible</b> even with Rx	

**Prognosis** Aggressive immunosuppressive therapy improves the prognosis. Class IV has the worst prognosis

**Other lines of Rx** IVIG, plasmapheresis, Rituximab (Anti-CD 20 monoclonal Ab)

# Juvenile Rheumatoid Arthritis

## Definition

It is a common rheumatic disease of children & a major cause of disability & blindness

## Etiology

- ☒ **Genetic predisposition:** HLA-DR4
- ☒ **Environmental factors:** Parvovirus B19, EBV

## Pathogenesis

- T-cell activation
- Release of mediators (TNF- $\alpha$ , IL-1, IL-6...)

JRA is a disease of synovium

## Pathology


### A) Arthritis

- Synovitis & Effusion
- Pannus formation: Active aggressive granulation tissue
- Cartilage destruction & bone erosion
- Fibrosis: ankylosis, deformity & subluxation

### B) Serositis

- Pleurisy
- Pericarditis

## Diagnostic Criteria of JRA

1. Age at onset < 16yrs
2. Arthritis in  $\geq 1$  joint 
3. Duration  $\geq 6$  wks
4. Onset **type** is defined by articular involvement in the 1<sup>st</sup> 6 months of onset
  - a. Polyarthritis  $\geq 5$  inflamed joints
  - b. Oligoarthritis < 5 inflamed joints
  - c. Systemic onset: Characteristic (spiky) fever
5. **Exclusion** of other causes of juvenile arthritis

### Arthritis:

- Swelling or effusion OR
- 2 of the following signs: hotness, tenderness,  
 $\downarrow$  range of movement, pain on motion

Not Red



## Clinical Picture

Morning stiffness (15-30 min), Easy fatigability, Joint pain  
 Joint swelling, hotness, tenderness but No redness

Oligoarthritis	Polyarthritis	Systemic-onset disease
<b>Types:</b> 1. Persistent oligo- 2. Extended oligo- ( $\rightarrow$ Poly-)	<b>Types:</b> 1. RF -ve* 2. RF +ve	- Daily spiky fever $\geq 2$ wks (high fever with <u>normal</u> intervals/day) - Characteristic macular rash (evanescent erythematous rash usually with the fever- trunk) - Arthritis may accompany or follow systemic manifestations - Koebner phenomenon = Cutaneous hypersensitivity to superficial trauma - Hip may be involved at the onset - HSM, LN - Pleurisy & pericarditis - Leukocytosis & thrombocytosis - ANA & RF +ve +ve - $\uparrow$ ESR
- Usually affecting joints of LL (Knee & ankle) - Asymmetric - Hip is almost never involved at the onset - Liable to chronic <b>uveitis</b> - ANA is +ve in 85-90%	- Usually affecting large & small joints of LL & UL (20) - Symmetric - Hip is almost never involved at the onset - T/M joint: Micrognathia - Atlantoaxial joint: subluxation - RF +ve type mimic adult form, with $\uparrow$ severity & $\uparrow$ deformities - ANA is +ve in 40-85%	
Uveitis may be asymptomatic	Quadriplegia	

## Differential Diagnosis

### 1. SOJRA Vs Leukemia (Fever pattern, site of pain, morning stiffness...)

	SOJRA	Leukemia
TLC	Usually $\geq 20,000$ (mainly PNL)	Usually $< 10,000$ (mainly lymphocytes)
Platelets	Thrombocytosis	Normal or $\downarrow\downarrow$
ESR	Markedly $\uparrow\uparrow$	

2. Acute rheumatic fever: (Red, migratory, asymmetric, evidence of recent Strept infection)

3. Post Streptococcal arthritis or arthralgia

4. Macrophage activation syndrome

**Etiology:** Complication of JRA precipitated by infections or drugs (e.g., NSAIDs...)

**C/P:** Fever, HSM, LN, Bleeding

**Investigations:**  $\downarrow\downarrow$  Platelets,  $\downarrow\downarrow$  Hb,  $\downarrow\downarrow$  TLC,  $\downarrow\downarrow$  Fibrinogen,  $\uparrow\uparrow$  FDPs

**Rx:** Steroids (Methylprednisolone), FFP, Stop NSAIDs

### Investigations (Diagnosis is mainly clinical)

#### A) Laboratory

- CBC: Anemia ( ), Thrombocytosis ( ), Leukocytosis ( )
- CRP & ESR:  $\uparrow\uparrow$  in activity
- ANA & RF
- Urinalysis, C<sub>3</sub> & C<sub>4</sub>: Normal

#### B) Imaging

- Slit-lamp examination is done every 3 months (in oligoarticular disease)
- X-ray: Soft tissue swelling, peri-articular osteopenia, bone erosions, deformities
- MRI cervical spine: atlanto-axial subluxation

#### C) Invasive

- Synovial fluid examination:  $\uparrow\uparrow$  Proteins &  $\uparrow\uparrow$  Cells (PNLs)

## Complications

1. Chronic uveitis
2. Joint deformities
3. Neurological
4. Short stature
5. Osteoporosis
6. Complications of Rx (Steroids, methotrexate, GH)
7. Psychological

- Uveitis is not related to the activity of arthritis (Slit lamp is **mandatory**)
- Uveitis is common with +ve ANA

#### Deformities in JRA:

- Ulnar deviation
- Swan-neck deformity
- Boutonniere
- Z-deformity of the thumb

## Treatment of JRA

### Golden Rule

Diagnose early, treat efficiently & be aggressive if indicated but do not forget side effects & growth & development

### Aim of Treatment

- ☒ Relief of pain
  - ☒ Control of inflammation
  - ☒ Prevent deformities
  - ☒ Preserve function
- } With minimal risk of side effects

### Rationale of Treatment

- ☒ Most of tissue destruction occurs in the 1<sup>st</sup> 2 yrs of disease onset
- ☒ It is not possible to predict the natural course of the disease at the onset

## A) Medical Treatment

### 1. NSAIDs

- **Action:** # Cyclo-oxygenase enzyme → ↓↓ PGs (i.e., Anti-inflammatory & analgesic)
- **Types**
  - COX-1 inhibitors (Ibuprofen, Naproxen)
  - COX-2 inhibitors (Celecoxib, Rofecoxib): Less side effects
- **Side effects**
  - GIT: Nausea, vomiting, abdominal pain
  - CNS: Mood changes, aseptic meningitis
  - Hepatic
  - Renal
- **Use in JRA:**
  - Anti inflammatory effect is achieved after ≈ 30 days of continuous use
  - In 20% of patients with JRA, NSAIDs are the only drug used to control arthritis

### 2. Hydroxychloroquine

- **Action:** Anti-malarial drug used as disease-modifying agent
- **Side effects**
  - Retinal toxicity: (Rare but serious)
  - BM suppression
- **Uses**
  - Cutaneous aspects of SLE
  - Dermatomyositis
  - ?JRA

200

Regular ophthalmologic ex. (Field of vision & color vision) is **mandatory** in patients receiving hydroxychloroquine

### 3. Sulfasalazine (= Salazopyrine)

- **Action:** Sulfasalazine = Sulphapyridine (Carrier) + 5-ASA (Anti-inflammatory)
- **Dose:** 50 mg/Kg/day
- **Indications**
  - Inflammatory bowel disease
  - Sero -ve spondyloarthropathies
  - JRA: ?Oligoarticular & Polyarticular disease
- **Side effects**
  - GIT: Nausea, vomiting, abdominal pain
  - Rash & Stevens-Johnson syndrome
- **Contraindications:**
  - G-6-PD deficiency
  - Porphyria

500

MTX is one of the cornerstone drugs in pediatric rheumatology

### 4. Methotrexate (*The safest, most effective & least toxic 2<sup>nd</sup> line of Rx*) ↗

- **Action:** # Dihydrofolate reductase → ↓↓ Purine synthesis (Anti-inflammatory)
- **Dose:** 5-10 mg/m<sup>2</sup>/week [Oral or better IM or SC]
- **Duration:** Not less than 1-2 yrs
- **Side effects** (Much milder than when used in neoplastic diseases)
  - GIT: Nausea, vomiting, abdominal pain, stomatitis
  - Hepatic: ↑↑ Liver enzymes, mild hepatic fibrosis
  - Lung fibrosis & teratogenicity
  - Add folic acid supplementation. Why?
- **Use in JRA:**
  - Specially in polyarticular disease (Response is expected not before 1 month)
  - Effective in 70-80% of patients

### 5. Gold: Not used now

6. **Leflunomide (Avara):** Not yet approved in children

7. **Steroids** (*Not used in all patients*)

- **Action:** Anti-inflammatory
- **Precautions:** Use the least dose for the least duration
- **Indications in JRA**
  - SOJRA (Pulse therapy: Methylprednisolone 10-30 mg/Kg/dose)
  - Polyarticular disease till the appearance of MTX effect "Bridging medication"
  - Macrophage activation syndrome
  - Uveitis: Topical steroids (+ pupillodilatation)
  - Intra-articular steroids (Triamcinolone): in oligoarthritis

8. **Biological Therapy**

- a. **Etanercept:** Anti TNF- $\alpha$  used in polyarticular disease
- b. **Infliximab:** Anti TNF- $\alpha$  used in SOJRA
- c. IL-1 receptor blocker (**Anakinra**)
- d. IL-6 receptor blocker

9. **Autologous HSCT**

10. **Vaccination**

- **Why:** Liable to infection
- **When:** Before start of immunosuppressive therapy

Contacts of immunocompromised children should not be given OPV

## **B) Physiotherapy**

- ☒ Muscle strengthening
- ☒ Range of motion exercises

## **C) Orthopedic surgery**

- ☒ Correction of deformities
- ☒ Joint replacement

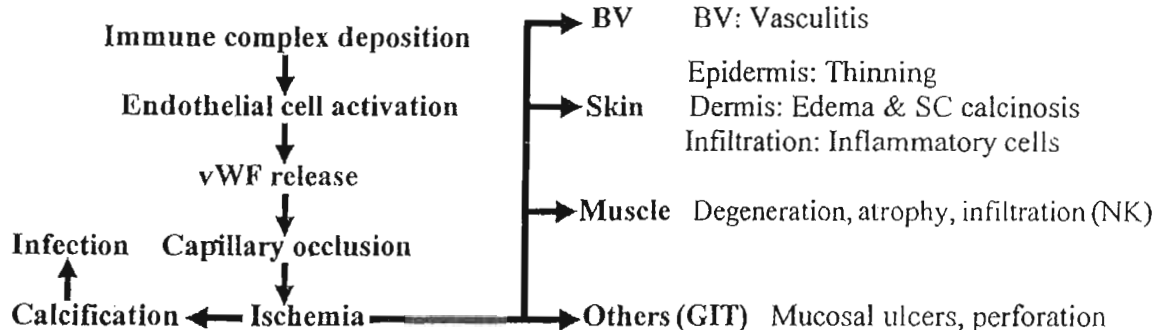
## **Management of different types of JRA**

# Juvenile Dermatomyositis

## Definition

It is chronic inflammatory disease characterized by small vessel vasculitis with involvement of the skin & striated muscle (inflammatory myopathy)

## Etiology & Pathology



## Clinical picture (Skin, Muscle, Others)

### A) Skin

- Heliotrope rash:** Violaceous rash over the upper eye lids
- Facial rash (Mask-like distribution) & photosensitivity**
- V-sign:** Erythematous rash in the exposed part of the chest
- Gottron papules:** Erythematous scaly rash over the knuckles & proximal I.P joints
- Calcinosis:** SC calcification (usually around knees & elbows)
- Partial baldness & facial edema**

### B) Muscle

- Skeletal muscle:** Proximal muscle weakness (inflammatory myopathy) "Describe"
- Smooth muscle:** Constipation, dysphagia & aspiration (palatorespiratory dysfunction)
- Cardiac muscle:** Conduction abnormalities & cardiomyopathy

### C) Others

- GIT:** Mucosal ulcers, perforation, melena
- Arthritis**
- Partial lipodystrophy:** Loss of SC fat → masculine appearance & acanthosis nigricans
- Fever, LN, HSM, renal impairment**

## Investigations

- ↑↑ Muscle enzyme (AST, CPK, LDH)
- EMG: irritability
- X-rays: SC calcification
- MRI: localizes active site of inflammation. Why?
- Muscle biopsy
- ↑↑ vWF & neopterin
- Nail-fold capillaroscopy

ESR is usually normal  
ANA (speckled) in 80% of children

## Treatment (prognosis is good in adequately treated patients)

- Cutaneous manifestation:** Avoid sun exposure & Sunscreen  
Hydroxychloroquine (3-5 mg/Kg/day)  
Prednisone (1 mg/Kg/day)
- Muscle disease:** Prednisone (1-2 mg/Kg/day) ± Pulse therapy... in severe cases  
Methotrexate (10-15 mg/m<sup>2</sup>/week Oral or better IM or SC) + folic acid  
Cyclophosphamide or cyclosporine in resistant cases
- Physiotherapy:** to prevent muscle contractures
- Palatorespiratory dysfunction:** Suction, NGT, ETT, tracheostomy

# Arthritis

## Definition

Inflammation of the synovial membrane of the joint

## Etiology

### A) Infection

#### 1. Septic arthritis

- ♂:♀ = 2:1
- Organism: Staphylococcus aureus & Hemophilus influenza
- Route: Try to septicemia, osteomyelitis or trauma
- Site: Knee, hip, ankle, elbow
- C/P: Redness, hotness, pain, swelling, loss of function
- Investigations: CBC, ESR, CRP, Blood culture, synovial fluid examination
- Imaging: X-ray, US, MRI, Bone scan
- Rx: Aspiration + antibiotics

#### 2. Osteomyelitis (with sympathetic joint effusion)

#### 3. Toxic synovitis of the hip joint

- Age: 2-8 yrs
- Etiology: Unknown (?following viral infection)
- C/P: Pain in the hip & limping [No or mild fever, No toxemia]
- Course: Self-limited (Resolution in 7-10 days)
- Rx: Rest, anti-inflammatory medications

Toxic synovitis is the most common cause of acute hip pain in children

#### 4. Reactive arthritis

- Definition: Arthritis following infection **outside** the joint (GIT, GU)
- Etiology: Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia
- Other causes: Rheumatic fever, Reiter syndrome, IBD
- Mechanism: Molecular mimicry
- C/P: Oligo- or polyarthritis

#### 5. Viral arthritis

- Definition: Arthritis following viral infection
- Etiology: EBV, CMV, HSV, VZV, HBV, Parvovirus B19

#### 6. Tuberculous arthritis

#### 7. Lyme disease

- Etiology: Borrelia burgdorferi
- C/P: Multisystem affection (FAHM, rash, arthritis, carditis, meningitis)
- Rx: Amoxycillin

### B) Rheumatic

#### 1. Rheumatic fever

#### 2. JRA

#### 3. SLE

#### 4. Sero -ve spondyloarthropathies

#### 5. Dermatomyositis

#### 6. Henoch-Schonlein purpura

#### 7. Inflammatory bowel disease

### C) Malignancy

#### 1. Leukemia

#### 2. Lymphoma

#### 3. Neuroblastoma

### D) Hematologic

#### 1. Sickle cell anemia

#### 2. Leukemia

#### 3. Hemophilia

### E) Metabolic

#### 1. Gout

#### 2. Alkaptonuria

### F) Traumatic

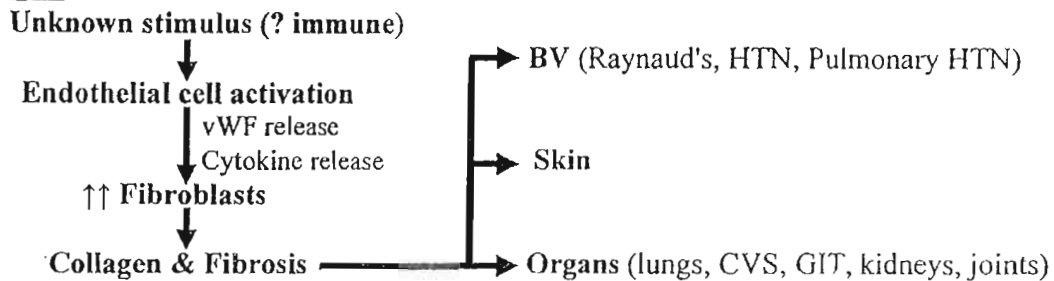


# Scleroderma (= Hard skin)

## Definition

It is chronic inflammatory disease characterized by excessive collagen deposition & fibrosis in the skin ± internal organs (lungs, CVS, GIT, kidneys, joints)

## Etiology



## Clinical picture (Classification of scleroderma)

### A) Localized scleroderma\* (No systemic manifestations)

#### Distribution:

- a. **Morphea:** Plaques
- b. **Linear**

Leg-length discrepancy

Early: edema & erythema

Later: hard, hairless, dry, pigmented, atrophic, adherent with contractures (related joint)

### B) Systemic sclerosis

#### a. **Cutaneous:** Diffuse skin affection

- Fingers: swollen, shiny, tapering with limited mobility (sclerodactyly)
- Face: mask face, fish mouth & wide nostrils (pinched nose)
- Feet
- Trunk

#### b. **Systemic:**

##### 1. **CVS:**

- Raynaud's phenomenon →
- Systemic hypertension
- Pericarditis, restrictive cardiomyopathy & arrhythmias

**Raynaud's phenomenon:** Triple sequence of color change  
[Pallor → Cyanosis → Redness]  
**Raynaud's disease:** Idiopathic

##### 2. **Lungs:**

- Hard skin
- Pleurisy
- Interstitial lung disease (restrictive hypoventilation)
- Pulmonary hypertension

##### 3. **GIT:**

- Esophagus: dysphagia
- Small intestine: stagnant loop (malabsorption)
- Large intestine: constipation

##### 4. **Kidneys:**

- Renovascular hypertension
- Hematuria, proteinuria, CRF

##### 5. **Joints:** arthritis (JRA-like)

#### **CREST syndrome:**

1. Calcinosis
2. Raynaud's phenomenon
3. Esophageal hypomotility
4. Sclerodactyly
5. Telangiectasia

### C) Eosinophilic fasciitis (Inflammation of the fascia with ↑↑ eosinophils)

### D) Secondary scleroderma (2ry to drugs e.g., Bleomycin)

### E) Pseudo-scleroderma (only cutaneous fibrosis)

**Investigations**

- Anti-SCL 70 & Anti-centromer Ab
- ↑↑ vWF & neopterin
- Nail-fold capillaroscopy
- CXR & HRCT chest
- Pulmonary function tests
- Echocardiography
- Esophageal motility study
- Urine analysis, KFTs

Anti-centromere Ab in scleroderma

**Treatment**

1. **Topical steroids:** Cutaneous lesions
2. **Systemic steroids & MTX:** Systemic scleroderma
3. **Physiotherapy:** to prevent muscle contractures
4. **Eosinophilic fasciitis:** Steroids
5. **Raynaud's phenomenon**
  - Avoid cold (Gloves)
  - Ca channel blockers (Nifedipine)
  - ACE inhibitors (Captopril)
  - Topical vasodilators (Nitroglycerine paste)
  - IV PGE1 (in severe cases)

**Mixed Connective Tissue Disease****(Overlap syndrome)****Definition**

It is a syndrome with combined features of SLE, JRA, Dermatomyositis & Scleroderma

**Investigations** Anti-ribonucleoprotein (Anti-RNP)

**Treatment** Steroids

**Sjogren Syndrome****Definition**

It is chronic inflammatory disease characterized by Lymphocytic infiltration of salivary & lacrima glands

**Clinical picture**

1. Xerophthalmia (Dry eyes): Photophobia & corneal ulcers
2. Xerostomia (Dry mouth): ↓↓ Taste, dental caries & ulcers
3. Parotid enlargement
4. Other collagen-vascular diseases (SLE, mixed CT disease...)

**Investigations**

- Schirmer test
- Anti-Ro & Anti-La antibodies
- Investigations of associated disease

**Treatment**

- Eye protection (Lubricant eye drops)
- Oral lozenges
- Steroids & other immunosuppressives

**Neonatal Lupus:**

**Mother:** SLE or Sjogren

**Cause:** Transplacental passage of maternal auto-Ab (Anti-Lo & Anti-La)

**C/P:**

- Congenital HB (Permanent)
- Cutaneous: Rash
- Hematological: Thrombocytopenia
- Hepatological: Hepatitis

**Rx:** Supportive + Steroids ± Pacemaker

# Amyloidosis

## Definition

Extra-cellular deposition of eosinophilic material in various tissues with 2ry organ dysfunction

## Pathology

Deposition of amyloid material can be:

- ☑ Localized (e.g., endocrinal organs with aging)
- ☑ Systemic (Primary, Familial, Dialysis-related, Secondary\*)

### Pathologic Types of amyloid

1. AA amyloidosis\*
2. AL amyloidosis

## Etiology

- A) **Primary:** Very rare in children (Cardiomyopathy & macroglossia)
- B) **Familial:** AD
- C) **Dialysis-related**
- D) **Secondary**
  - 1. **Familial Mediterranean fever**
  - 2. **Multiple myeloma**
  - 3. **Chronic diseases**
    - a. **Chronic Infection** [TB, CF, Suppurative lung diseases]
    - b. **Chronic Inflammation** [JRA, JAS, IBD]

## Clinical Picture (Onset > 10 yrs)

- Picture of the cause (FMF, JRA, IBD...)
- Renal dysfunction\* [Proteinuria, NS, renal failure]
- Others: Abdominal pain, diarrhea, malabsorption, anemia, HSM



## Diagnosis

- Picture of the cause
- Biopsy + Congo red staining [Rectal or gingival biopsy]
- Evaluation of renal function (UA, A/C ratio, KFTs)

## Treatment

- FMF: Colchicine (↓↓ attacks & ↓↓ development of amyloidosis)
- JRA: Chlorambucil (↑↑ Risk of malignancy)

# Familial Mediterranean fever

## Etiology

AR<sup>16</sup> disease due to mutation of the MEFV gene (there are > 50 known mutations)

## Clinical Picture (Onset < 5 yrs)

- Acute episodes of
  - Fever
  - Synovitis: arthritis/arthralgia
  - Serositis: Peritonitis, pleurisy, pericarditis
- Other manifestations: Skin rash, myalgia, scrotal pain, HSM
- Picture of amyloidosis:



## Diagnosis (Mainly clinical diagnosis)

- Genetic studies (Only 5-10 mutations are usually screened)
- Picture of amyloidosis (in 40-50% of patients)

## Treatment

- Colchicine (↓↓ attacks & ↓↓ development of amyloidosis): 0.02-0.03 mg/Kg/day
- Renal replacement therapy (Dialysis & transplantation)

# **Hereditary Periodic Fever Syndromes**

(Human auto-inflammatory syndromes)

## **Definition**

Group of hereditary disorders characterized by:

- Self-limited
- Genetic defects (AD or AR)
- Recurrent episodes of fever associated with inflammatory manifestations
- Secondary amyloidosis

## **Classification**

1. FMF
2. Tumor necrosis factor-receptor-associated periodic syndrome (TRAPS)
3. Hyperimmunoglobulinemia D syndrome (HIDS)
4. Muckle-Wells syndrome
5. Familial cold urticaria
6. Periodic fever, adenopathy, pharyngitis & aphthous stomatitis (PFAPA)
7. Cyclic neutropenia

## **Clinical Picture**

- Acute episodes of variable combination of:
  - Fever
  - Arthritis/arthralgia
  - Abdominal pain, chest pain
  - Rash, conjunctivitis, LN

# **Behcet Disease**

## **Etiology**

- ☒ Unknown
- ☒ Genetic factors: Association with HLA-B5 & HLA-B51

## **Clinical Picture** (Rare in children)

- Recurrent oro-genital ulcers
- Uveitis
- Pathergy: Sterile pustule following a needle prick
- Arthritis
- Thrombosis: Large vessels (SVC, IVC, Budd-Chiari syndrome...)

## **Treatment**

- Colchicine
- Steroids

# Spondyloarthropathies

## General Features

- Sero -Ve
- No SC nodules
- Familial tendency ( $\sigma > \varphi$ )
- HLA-B27
- Enthesopathy (= Inflammation at site of attachment of Ligaments, Tendons, Fascia, Capsules to bones)
- Sacro-ileitis & spondylitis (Low-back pain)
- Peripheral arthritis:
  - LL > UL
  - Asymmetric

## Types

- Juvenile ankylosing spondylitis
- Psoriatic arthritis
- Arthritis with IBD
- Reactive arthritis

## Etiology

Unknown

## Pathology

Synovitis, & Enthesitis

## Types & C/P

	Juvenile ankylosing spondylitis	Psoriatic arthritis	Arthritis with IBD	Reactive arthritis
Arthritis	<b>2 Patterns:</b> A) Peripheral Oligoarthritis - LL > UL (Hip joint) - Proximal > Distal joints B) Spondyloarthritis - Associated with HLA-B27 - ?-shaped	<b>2 Patterns:</b> A) Peripheral Oligoarthritis - Small & large joints - Distal IP joints B) Spondyloarthritis - Associated with HLA-B27	<b>2 Patterns:</b> A) Peripheral polyarthritis - Related to IBD activity - Negative HLA-B27 B) Spondyloarthritis - Not related to IBD activity - Associated with HLA-B27	<b>2 Patterns:</b> A) Peripheral Oligoarthritis - LL > UL - Asymmetric B) Spondyloarthritis - Associated with HLA-B27
Other Features	■ Enthesitis (Localized tenderness) ■ Iritis ■ Aortic regurg	Nail pitting, dactylitis, onycholysis, +ve family history of psoriasis	IBD (Chron & Ulcerative colitis)	<b>Reiter's syndrome:</b> Arthritis, conjunctivitis & urethritis

**Diagnosis** Old ♂ child with oligoarthritis & enthesitis with later involvement of the axial skeleton (Sacro-ileitis) & loss of spine flexibility

**X-ray** Loss of lumbar lordosis, Bamboo spine, pseudo-widening of sacroiliac joint

**DD** Low back pain

**Treatment** NSAIDs, sulfasalazine, physiotherapy, psychological

## Causes of low back pain:

1. IAS & other Spondyloarthropathies
2. Septic arthritis of the S/I joint
3. Osteomyelitis of the pelvis or the spine
4. Tumors (osteosarcoma, Ewing, leukemia...)
5. Trauma

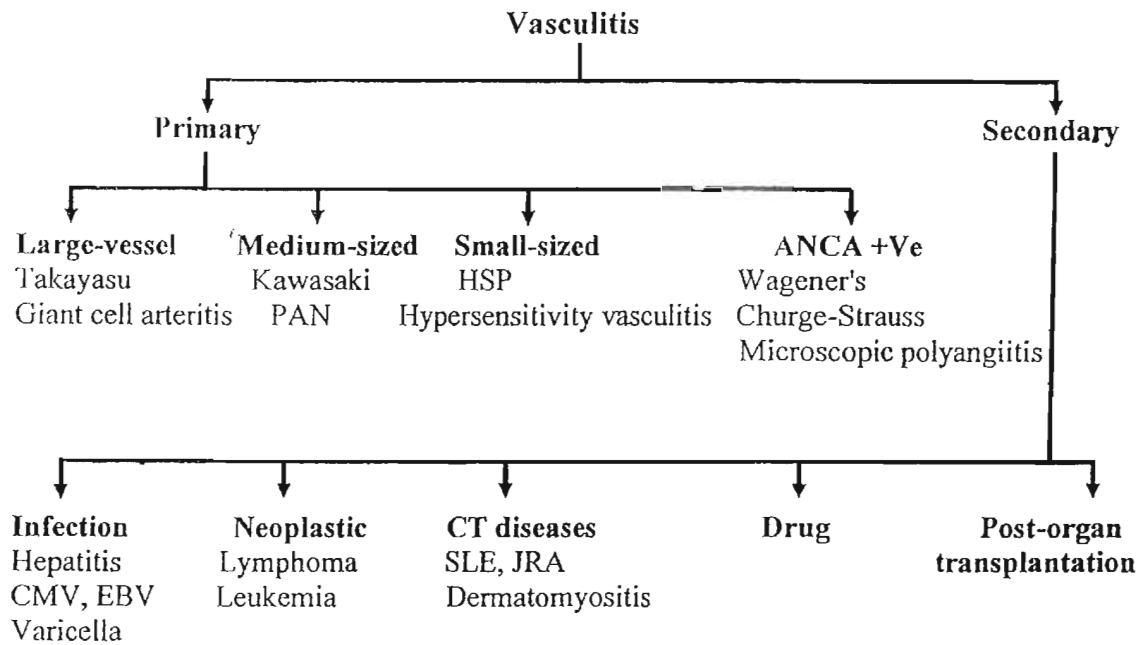
# Vasculitis Syndromes

## Definition

Group of disorders characterized by inflammation of BVs. It is not that simple:

- Variability of BV that may be involved
- Variability of the ways of involvement
- Variability of the involved tissues & organs

## Classification



## Clinical Picture

- Early in the course, the findings may be nonspecific (FHAM)
- With progression, specific manifestations become apparent
- C/P varies according to the involved BV
  - ☑ Medium & large-sized
    - Chest pain, claudication & HTN
    - Abdominal pain
    - Absent or weak pulses
  - ☑ Small-sized BV
    - Skin: Purpuric eruption (rash)
    - Renal: Hematuria, HTN
    - GIT: Abdominal pain & bleeding
    - Joint: Arthritis
    - Lungs: Hemoptysis

Early diagnosis & Rx is important to prevent permanent tissue damage

## Approach to Diagnosis

2 Windows on small BV



# Henoch-Schonlein Purpura

## (Anaphylactoid purpura)

### Definition

It is small-vessel vasculitis mainly affecting skin, GIT, joints & kidneys

### Epidemiology

It is the most common pediatric vasculitis

♂: ♀ = 2:1

### Etiology

Post-infectious (Group A Streptococci\*)

### Pathology

- Site: Skin, GIT, joints & kidneys
- Type: Small-vessel vasculitis
- Nature: IgA-mediated process

Renal involvement is the major complication of HSP

### Clinical Picture

#### 1. Skin

- Occurs in 100% of patients
- Purpuric eruption mostly on the LL & buttocks, sparing the trunk & the back

#### 2. Arthritis

- Occurs in 70% of patients
- Usually affecting large joints (knees & ankles) with spontaneous resolution within days

#### 3. GIT

- Occurs in > 50% of patients
- Abdominal pain, bleeding (hematemesis & bleeding per rectum), intussusception, perforation

#### 4. Nephritis

- Occurs in 25-50% of patients (Early\* in the course or may be delayed)
- Hematuria, proteinuria, NS, HTN, RPGN, CRF (1%)

F/U is needed for 6 months

#### 5. Other manifestations

- CNS: Seizures, coma, blindness
- Testicular: Swelling & torsion

### Investigations

- CBC (anemia??), ↑↑ ESR
  - Urine analysis, KFTs
  - Skin biopsy
  - Renal biopsy
- } IgA-deposition

### DD

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>▪ <b>Rash:</b> Purpura, Meningococemia</li> <li>▪ <b>Arthritis:</b> See before</li> </ul> | <ul style="list-style-type: none"> <li>▪ <b>GIT:</b> Bleeding</li> <li>▪ <b>Nephritis:</b> Hematuria</li> </ul> |
|--|---|

### Treatment

1. **NSAIDs:** Pain, arthritis, fever
2. **Steroids** (Prednisone 1-2 mg/Kg/day): GIT or Renal disease
3. **Immunosuppressive** (Cyclophosphamide or azathioprine): in severe cases; RPGN
4. **Rx of Complications:** Renal failure, intussusception, bowel perforation

# Takayasu Arteritis

## (Pulseless disease)

### Definition

It is large-vessel vasculitis mainly affecting aorta & its major branches

### Pathology

Segmental panarteritis → Stenosis & aneurysmal dilatation → Rupture

### Clinical Picture

- Constitutional manifestations: FHAM
- Weak (Absent) pulses
- Renal: HTN
- Cardiac: HTN, Cardiomyopathy
- CNS: Ischemia (Deficits)

### Investigations

- CBC (anemia), ↑↑ ESR
- Echocardiography
- Doppler, MRA, angiography

### Treatment

- Steroids, cyclophosphamide, MTX
- Rx of HTN & HF
- Aortic dilatation (aneurysm): Excision + Graft

# Polyarteritis Nodosa

### Definition

It is medium-vessel vasculitis

### Epidemiology

It is the 1<sup>st</sup> discovered vasculitis (1866)

♂:♀ = 1:1

### Etiology

Post-infectious (HBV, HCV, TB, CMV, Strept.)

### Pathology

- Necrotizing vasculitis
- Aneurysm formation

### Clinical Picture

1. **Skin:** Purpura, rash, Raynaud's phenomenon
2. **Arthritis**
3. **GIT:** Abdominal pain, bleeding (hematemesis & bleeding per rectum)
4. **Nephritis:** Hematuria, proteinuria, NS, HTN
5. **Other manifestations**
  - CNS: Seizures, coma, blindness
  - Testicular: Swelling & torsion

### Investigations

- CBC (anemia), ↑↑ ESR
- Doppler, MRA, angiography

Treatment Steroids, cyclophosphamide



## ANCA-associated Vasculitides

### A) Wegener Granulomatosis

(Lethal Midline granuloma)

#### Definition

It is destructive granulomatous lesion of the upper respiratory tract & lungs  
AND systemic small-medium-vessel vasculitis mainly affecting lungs & kidneys

#### Etiology

Unknown

#### Pathology

- Necrotizing granuloma
- Alveolar hemorrhage
- Crescentic GN
- Vasculitis

#### Clinical Picture

- Constitutional manifestations: FHAM
- Upper respiratory tract: Nasal obstruction & discharge & sinusitis
- Lungs: Cough, dyspnea & hemoptysis
- Kidneys: Hematuria, proteinuria, RPGN, CRF

#### Investigations

- CBC (anemia), ↑↑ ESR
- ANCA (towards PR3) = cANCA
- Urine analysis, KFTs
- CXR, X-rays Nose & sinuses
- HRCT chest
- Renal & lung biopsy

Treatment Steroids, cyclophosphamide

### B) Microscopic polyangiitis

#### Definition

Small-vessel vasculitis mainly affecting lungs & kidneys

#### Clinical Picture

- Lungs: Hemoptysis
- Kidneys: Hematuria & Proteinuria

Treatment Steroids, cyclophosphamide

### C) Churge-Strauss Syndrome

#### Definition

Small-vessel vasculitis

#### Clinical Picture

- Vasculitis
- Asthma

Investigations ↑↑ Eosinophils

Treatment Steroids, cyclophosphamide

Generic Name	Trade Name	Route	Dose mg/Kg/dose	Frequency
Paracetamol	Paracetamol, Pyral, Cetal	PO, Rectal, IV	10-15	4-6 hrs
Ibuprofen	Brufen, Marcofen	PO, Rectal	10-15	6-8 hrs
Ketoprofen	Ketofan	PO, Rectal	0.5-1	6-8 hrs
Acetylsalicylic acid	Aspirin, Aspegic	PO, Rectal, IV	10-15	4-6 hrs
Diclofenac	Voltaren	PO, Rectal	0.5-1	6-8 hrs
Metamizole	Novalgin	PO, Rectal	10-15	6-8 hrs
Mefenamic acid	Ponstan	PO	5	6-8 hrs
Nimesulide	Sulide	PO	2-3	6-8 hrs

### Remember

- Paracetamol is the **safest** antipyretic in infants and children
- Paracetamol & ibuprofen should be the 1<sup>st</sup> choice in children
- Acetylsalicylic acid (Aspirin) should not be used in infants (Metabolic disturbances)
- Paracetamol is the safest antipyretic to be given in patients with G-6-PD deficiency
- Patients with G-6-PD deficiency should not receive acetylsalicylic acid or novalgin
- Side effects of NSAIDs (Ibuprofen, Ketoprofen, Diclofenac): Gastric irritation & ulcers, bleeding tendency, exacerbation of asthma, decrease renal blood flow

### C) Specific Treatment

- ☑ Antibiotics should be used only for specific bacterial infections
- ☑ Type of antibiotics: Depends on the clinical diagnosis & results of investigations
- ☑ Route & Duration
  - Simple infections: Oral antibiotics for 5-7 days
  - Serious infections: Combined parenteral antibiotics for 10-14 days

## Antibiotics in Pediatric Practice

Penicillins		Comments
Benzyl penicillin	Penicillin G	Gram +Ve organisms (IM, IV)
Phenoxymethyl Penicillin	Penicillin V	Gram +Ve organisms (Oral)
Penicillinase-resistant penicillins	Cloxacillin	Gram +Ve organisms
Broad spectrum	Ampicillin	Broad spectrum
Antipseudomonal penicillin	Piperacillin	Antipseudomonal
Cephalosporins		
1 <sup>st</sup> generation	Cephalexin	Gram +Ve organisms
2 <sup>nd</sup> generation	Cefaclor	Broad spectrum
3 <sup>rd</sup> generation	Cefotaxime	Gram -Ve organisms
Aminoglycosides		
Gentamicin, Amikacin, Tobramycin		Gram -Ve organisms + Anti-Staph.
Macrolides		
Erythromycin, Spiramycin, Clarithromycin, Azithromycin		Gram +Ve organisms
Others: Chloramphenicol, Co-trimoxazole, Clindamycin, Vancomycin, Imipenem		

# Kawasaki Disease

## (Mucocutaneous LN syndrome)

### Definition

It is acute febrile vasculitis involving medium-sized vessels with special predilection of the coronaries. Kawasaki is a **unique** vasculitis:

3

- Disease of childhood (80% < 5yrs)
- Clinical diagnosis
- Self-limited

### Etiology

- ☑ Genetic factors: More common in Asians
  - ☑ Infections: Occurs in epidemics
- } Immune-mediated

### Diagnostic Criteria of KD

3

1. Fever  $\geq 5$  days
2. The presence of  $\geq 4$  out of 5
  - a. Bilateral conjunctival injection (Not purulent)
  - b. Dry fissured lips, strawberry tongue, injected pharynx
  - c. Extremities:
    - Acute phase: Erythema/edema in hands & feet
    - Subacute phase: Periungual desquamation
  - d. Rash: Polymorphic (Not vesicular) mainly on the trunk
  - e. Cervical LN  $> 1.5$  cm (usually unilateral)
3. Exclusion of other diseases with similar findings

- Patients with fever  $\geq 5$  days &  $< 4/5$  can be diagnosed as KD if they have coronary affection
- Diagnosis can be made before the 4<sup>th</sup> day if there are  $\geq 4/5$

**Incomplete or atypical KD =**  
Fever  $\geq 5$  days but with  $< 4/5$

### Other Clinical Manifestations

1. CVS:
  - Cardiac involvement (50%)
    - Myocarditis
    - Pericarditis
    - Coronary artery aneurysm (25% of patients, risk is  $\uparrow\uparrow$  in infants)
    - Myocardial ischemia & infarction
  - Raynaud's phenomenon
2. CNS
  - Irritability
  - Aseptic meningitis
3. GIT:
  - Hepatitis
  - Abdominal pain & diarrhea
4. Joints: arthritis

### Clinical Phases

	Duration	Main features
A) Acute febrile phase	1 <sup>st</sup> 1-2 wks	Fever, myocarditis, erythema
B) Subacute phase	Till the 4 <sup>th</sup> wk	Desquamation, coronary aneurysm
C) Convalescent phase	Till 6 <sup>th</sup> -8 <sup>th</sup> wks	No clinical signs only $\uparrow\uparrow$ ESR & +ve CRP

### DD

- Measles (Koplik spots)
- Scarlet fever
- Toxic shock syndrome
- SOJRA
- EBV infection
- Stevens-Johnson & Toxic epidermal necrolysis

## Investigations (Diagnosis is mainly clinical)

### A) Laboratory

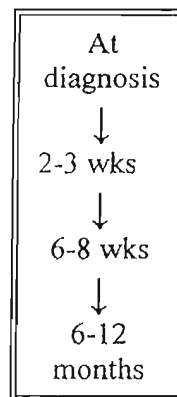
- CBC: Anemia, Thrombocytosis (Up to  $> 1.000.000/\text{mm}^3$ ), Leukocytosis
- CRP & ESR:  $\uparrow\uparrow$
- Liver enzymes:  $\uparrow\uparrow$
- Urinalysis: Sterile pyuria
- CSF: Pleocytosis

### B) Imaging

- CXR
- Echocardiography (Coronary internal diameter  $> 3\text{mm}$  is significant) **When?**
- [NB: Giant coronary artery aneurysm  $\geq 8\text{ mm}$  internal diameter]

### C) Invasive

- Coronary angiography



## Treatment

### A) Acute febrile phase

- **IVIG:** 2 g/Kg over 10-12 hrs AND
- **Aspirin:** 80-100 mg/Kg/day qid for 14 days

### B) Convalescent phase

- **Aspirin:** 3-5 mg/Kg/day once qid till 6-8 wks after the onset of the disease

### C) Acute coronary thrombosis

- Streptokinase, urokinase, tissue plasminogen activator (rTPA)

### D) Long-term therapy for patients with coronary abnormalities

- **Regular F/U:** Echocardiography  $\pm$  angiography  $\pm$  Intervention (stent)  $\pm$  bypass
- **Small solitary aneurysm:** Continue aspirin for life...
- **Large or multiple aneurysms:** Warfarin or LMW heparin

### E). Refractory KD

- Retreatment with IVIG (2-3 times)
- Pulse methylprednisolone
- Infliximab

Annual influenza vaccination

- Male sex
- Age  $< 1\text{yr}$
- Prolonged fever
- Recurrence of fever
- $\downarrow\downarrow$  Hb,  $\downarrow\downarrow$  PLT,  $\downarrow\downarrow$  Albumin

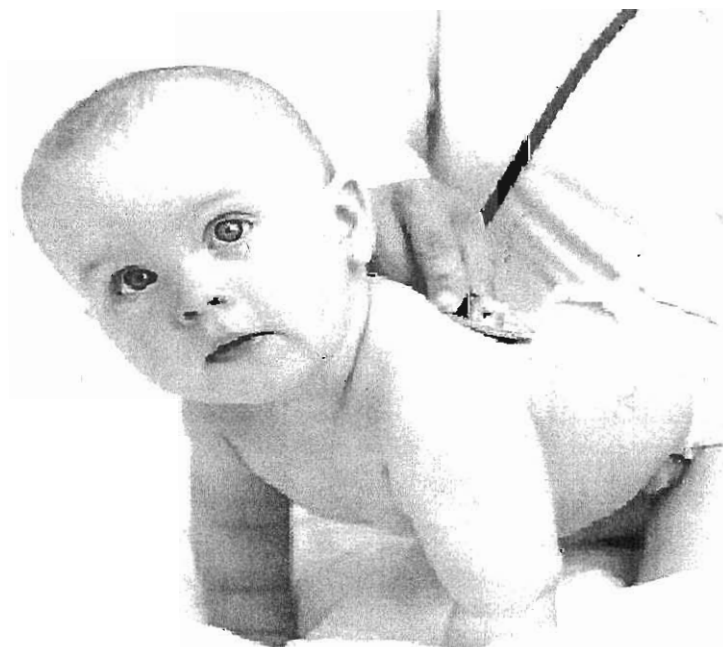
## Prognosis

1. Predictors of poor outcome **Score 0-2/3/4/5**
2. Complete recovery: If no coronary involvement
3. Coronary aneurysm: Spontaneous resolution in 1-2 yrs
4. Giant coronary aneurysms: Unlikely to resolve (Thrombosis, stenosis, ischemia, infarction)
5. Recurrence: 1-3%
6. Mortality = 0.01% (In Japan)

# Complementary Topics

*Pediatrics Master* 2013

*2<sup>nd</sup> Part Exams*



W  
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*Good luck*

# Pediatric master

2<sup>nd</sup> part exam

Complementary topics

IMAD ATTIA  
2013



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Faculty of Medicine

# BOYS

## Egyptian Growth Charts 2002

(2 - 21 years)



جامعة القاهرة  
Cairo University

**Source:** Cairo University, Diabetic Endocrine and Metabolic Pediatric Unit and the National Research Centre - Cairo, in collaboration with Wright State University, School of Medicine, Department of Community Health Lifespan, Health Research Center. From a total sample size of 33189 girls & boys (birth - 21 years):

- 13533 boys, for stature from 2 - 21 years
- 13703 boys, for weight from 2 - 21 years
- 13507 boys, for BMI from 2 - 21 years.

### How to measure:

**Weight:** from birth - 2 years, a boy should always be weighed naked on an appropriate, self-calibrating or regularly calibrated scale. An older boy should be weighed with his underwears. Record to the nearest 0.1 kg.

**Head circumference:** head circumference measurement should be taken from midway between the eyebrows and the hairline at the front of the head and the occipital prominence at the back. Appropriate thin plastic tape should be used.

**Supine length:** from birth to 2-3 years, a boy should be measured on his back by 2 people with appropriate equipment featuring a headboard and movable footboard. Whilst one person holds the head against the headboard, with the head facing upwards in the Frankfurt plane\*, a second person measures the length by bringing the footboard up to the heels. Ensure that the legs are flat at the knee joints.

**Standing height:** from approximately 2-3 years onwards, standing height should be measured against an appropriate vertical measure. The heels should be together with the buttocks and shoulder blades touching the vertical and the head positioned in the Frankfurt plane\*. To ensure that the true height is taken, apply gentle upward pressure to the mastoid processes.

Record head circumference, length and height to the nearest 0.1 cm

\* The Frankfurt plane is an imaginary line from the center of the ear hole to the lower border of the eye socket

### Body Mass Index (BMI):

To calculate the BMI, apply the following formula:

$$BMI = \frac{\text{weight in kg}}{(\text{length / height in m})^2}$$

Date	Age	*	Measurement	Name
14/03/03	9.5	H	136	
14/03/03	9.5	W	40	
14/03/03	9.5	BMI	21.6	

### How to Calculate the Target Centile Range (TCR):

From age 2 years onwards, if every boy follows his genetic growth pattern, he should be growing within his Target Centile Range (TCR) parallel to one of the centile lines. If not, refer to specialist. To calculate his TCR, apply the following steps: measure father's and mother's heights (a & b), calculate the sum (c), their mean height (d), the corrected Mid-Parental Height (MPH) (e) and the Target Centile Range (f) as shown. Apply arrow (e) opposite the corrected MPH, and draw a vertical line above and below, opposite the TCR

### Guidelines for recording, plotting and referral:

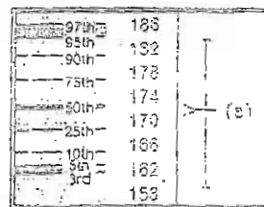
Record the measurements using the boxes included in this chart. Enter the date and the current age, specify the measurement in the box below the asterisk (i.e. H/C = Head circumference, L = Length, W = Weight, H = Height, BMI = Body mass index) and put your name. Plot each measurement on the curve with a well defined dot. Trace the growth curve with a line but leave the dots clearly visible. A normal growth curve is one that always runs roughly on, or parallel to one of the printed centile lines. If it doesn't, consider these guidelines:

Refer a boy whose height falls above the 97<sup>th</sup> or below the 3<sup>rd</sup> centile line or outside his Target Centile Range (TCR). Refer him, also if, in the pre-school age, his growth curve deviates upwards, or downwards, over a period of 12-18 months, by a width of one centile distance or, in the school age, by 2/3 of a centile distance.

Refer a boy whose Body Mass Index (BMI) equal or above 95<sup>th</sup> centile as obese. Boys with BMI equal or above the 85<sup>th</sup> centile but less than the 95<sup>th</sup> centile, should be considered as overweight. Also, refer a boy whose BMI falls below the 3<sup>rd</sup> centile as significantly underweight.

- (a) = Father's height
- (b) = Mother's height
- (c) = Sum of (a) and (b)
- (d) = (c) ÷ 2
- (e) = (d) + 7 cm = (MPH)
- (f) = MPH ± 12 cm

(a) =	174 cm
(b) =	156 cm
(c) =	330 cm
(d) =	165 cm
(e) =	165 + 7 = 172 cm
(f) =	172 ± 12 cm



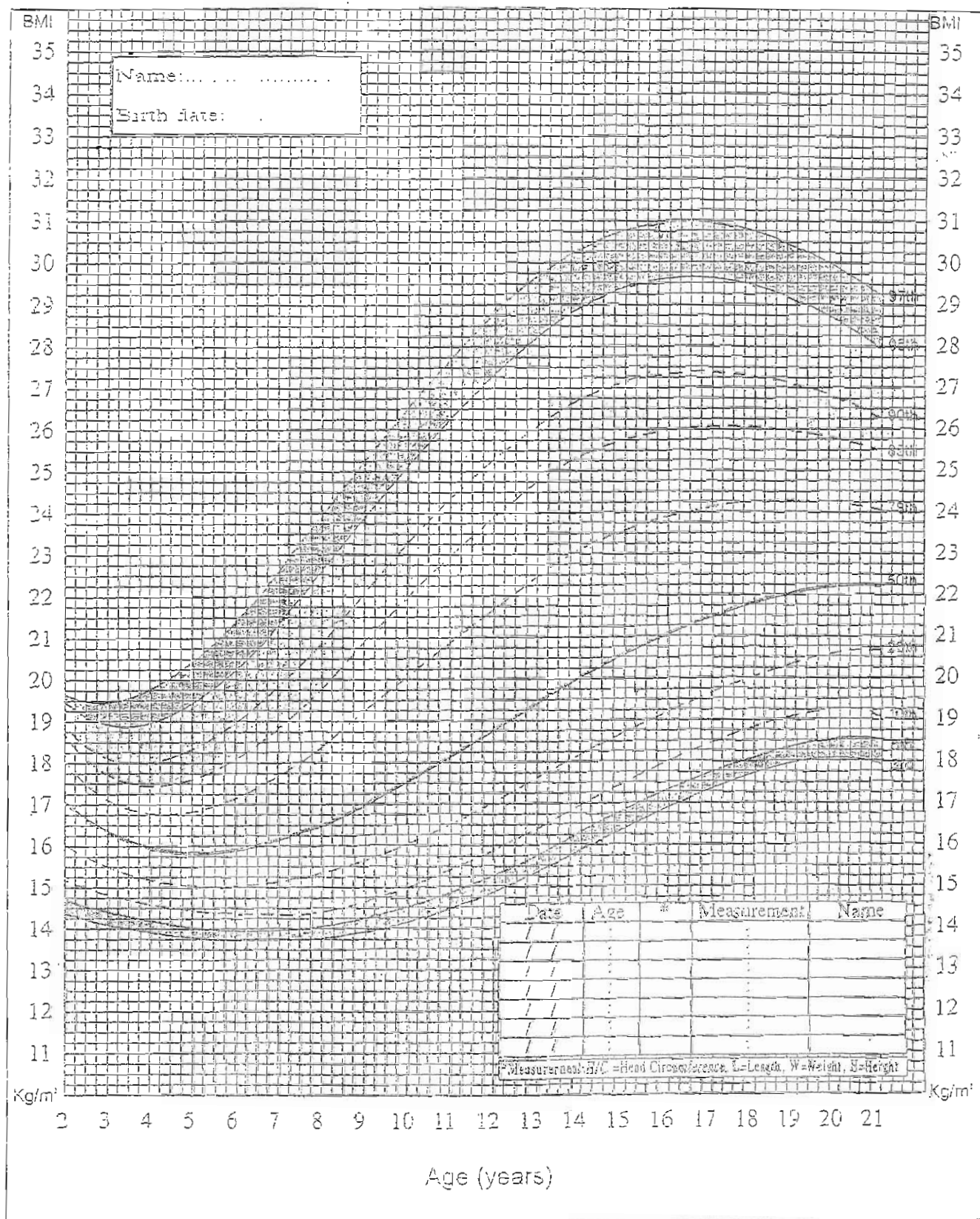
### Acknowledgments:

The Egyptian Supreme Council of Universities, Foreign Relations Coordination Unit (FRCU) - Mendez England & Associates, Cairo - The Egyptian Ministry of Education - The Egyptian Participating Schools and Universities.

Diabetes, Endocrine and metabolism Pediatric Unit (D.E.M.P.U)

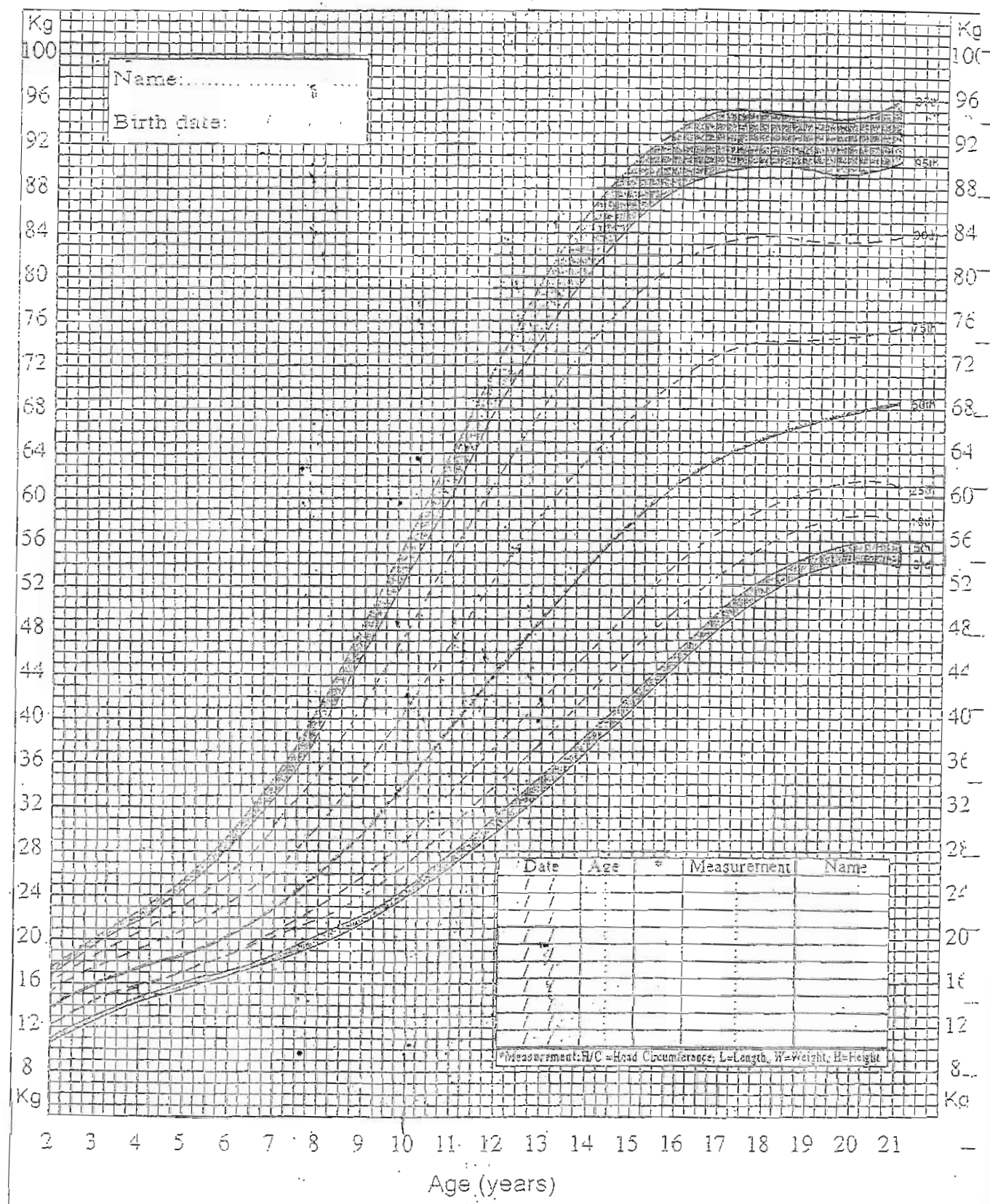


# Body Mass Index-for-Age Percentiles: Egyptian Boys, 2 to 21 years

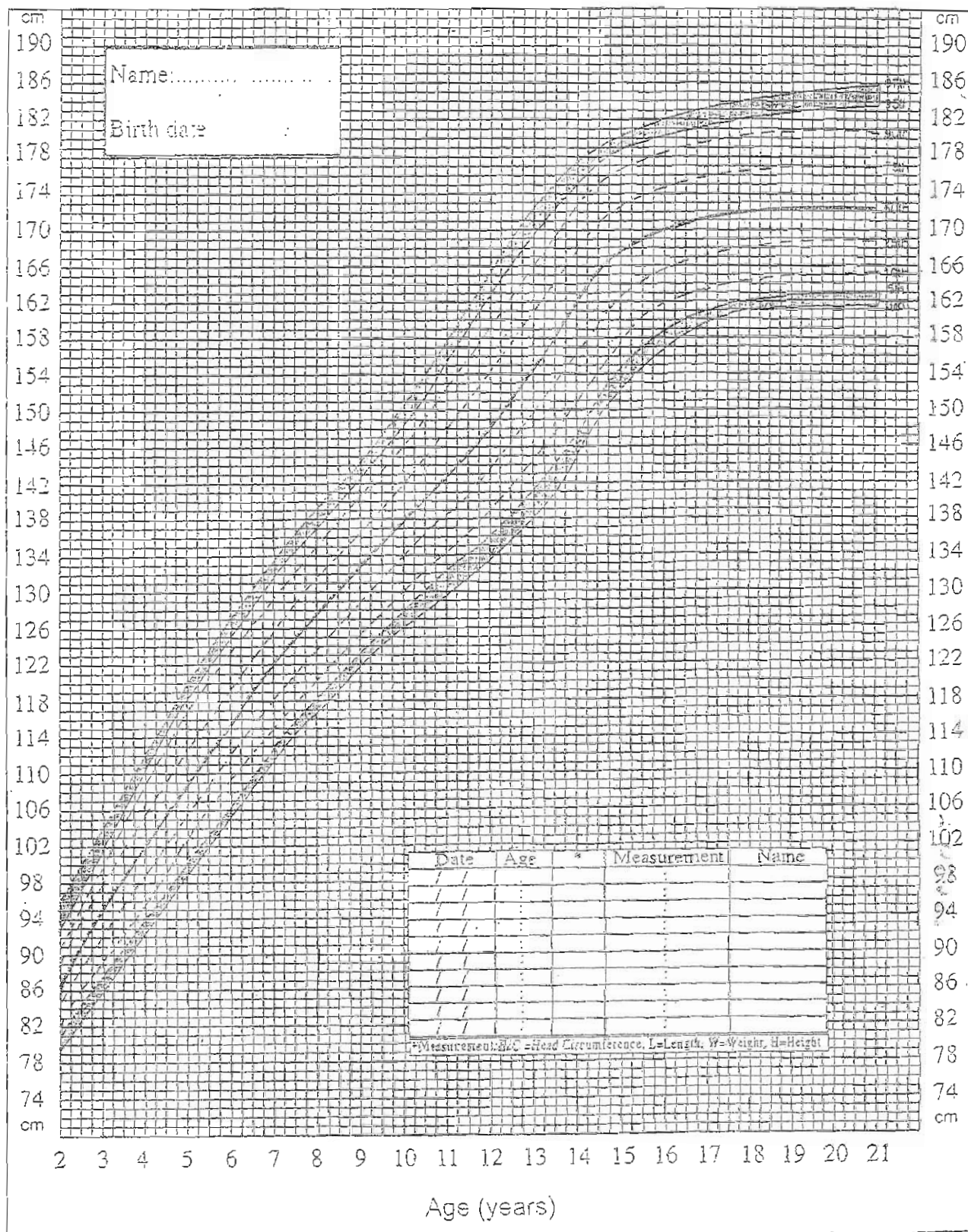


Price : 2.5 L.E

# Weight-for-Age Percentiles: Egyptian Boys, 2 to 21 Years



# Stature-for-Age Percentiles: Egyptian Boys, 2 to 21 Years







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# GIRLS

## Egyptian Growth Charts 2002

### (2 - 21 years)



جامعة القاهرة  
Cairo University

**Source:** Cairo University. Diabetic Endocrine and Metabolic Pediatric Unit and the National Research Centre - Cairo, in collaboration with Wright State University. School of Medicine. Department of Community Health Lifespan. Health Research Center. From a total sample size of 33189 girls & boys (birth - 21 years):

- 13533 boys, for stature from 2 - 21 years
- 13703 boys, for weight from 2 - 21 years.
- 13507 boys, for BMI from 2 - 21 years.

#### How to measure:

**Weight:** from birth - 2 years, a boy should always be weighed naked on an appropriate, self-calibrating or regularly calibrated scale. An older boy should be weighed with his underwears. Record to the nearest 0.1 kg.

**Head circumference:** head circumference measurement should be taken from midway between the eyebrows and the hairline at the front of the head and the occipital prominence at the back. Appropriate thin plastic tape should be used.

**Supine length:** from birth to 2-3 years, a boy should be measured on his back by 2 people with appropriate equipment featuring a headboard and moveable footboard. Whilst one person holds the head against the headboard, with the head facing upwards in the Frankfurt plane\*, a second person measures the length by bringing the footboard up to the heels. Ensure that the legs are flat at the knee joints.

**Standing height:** from approximately 2-3 years onwards, standing height should be measured against an appropriate vertical measure. The heels should be together with the buttocks and shoulder blades touching the vertical and the head positioned in the Frankfurt plane\*. To ensure that the true height is taken, apply gentle upward pressure to the mastoid processes. Record head circumference, length and height to the nearest 0.1 cm.

\* The Frankfurt plane is an imaginary line from the center of the ear hole to the lower border of the eye socket.

#### Body Mass Index (BMI):

To calculate the BMI, apply the following formula:

$$BMI = \frac{\text{weight in kg}}{(\text{length / height in m})^2}$$

Date	Age	"	Measurement	Name
14/03/03	9.5	H	135	
14/03/03	9.5	W	40	
14/03/03	9.5	BMI	21.6	

#### How to Calculate the Target Centile Range (TCR):

From age 2 years onwards, if every boy follows his genetic growth pattern, he should be growing within his Target Centile Range (TCR) parallel to one of the centile lines. If not, refer to specialist. To calculate his TCR, apply the following steps: measure father's and mother's heights (a & b), calculate the sum (c), their mean height (d), the corrected Mid-Parental Height (MPH) (e) and the Target Centile Range (f) as shown. Apply arrow (e) opposite the corrected MPH, and draw a vertical line above and below, opposite the TCR.

#### Guidelines for recording, plotting and referral:

Record the measurements using the boxes included in this chart. Enter the date and the current age, specify the measurement in the box below the asterisk (i.e. H/C = Head circumference, L = Length, W = Weight, H = Height, BMI = Body mass index) and put your name. Plot each measurement on the curve with a well defined dot. Trace the growth curve with a line but leave the dots clearly visible. A normal growth curve is one that always runs roughly on, or parallel to one of the printed centile lines. If it doesn't, consider these guidelines:

Refer a boy whose height falls above the 97<sup>th</sup> or below the 3<sup>rd</sup> centile line or outside his Target Centile Range (TCR). Refer him, also if, in the pre-school age, his growth curve deviates upwards, or downwards, over a period of 12-13 months, by a width of one centile distance or, in the school age, by 2/3 of a centile distance.

Refer a boy whose Body Mass Index (BMI) equal or above 95<sup>th</sup> centile as obese. Boys with BMI equal or above the 85<sup>th</sup> centile but less than the 95<sup>th</sup> centile, should be considered as overweight. Also, refer a boy whose BMI falls below the 3<sup>rd</sup> centile as significantly underweight.

- (a) = Father's height
- (b) = Mother's height
- (c) = Sum of (a) and (b)
- (d) = (c) ÷ 2
- (e) = (d) + 7 cm = (MPH)
- (f) = MPH ± 12 cm

(a) =	174 cm
(b) =	156 cm
(c) =	330 cm
(d) =	165 cm
(e) =	165 + 7 = 172 cm
(f) =	172 ± 12 cm

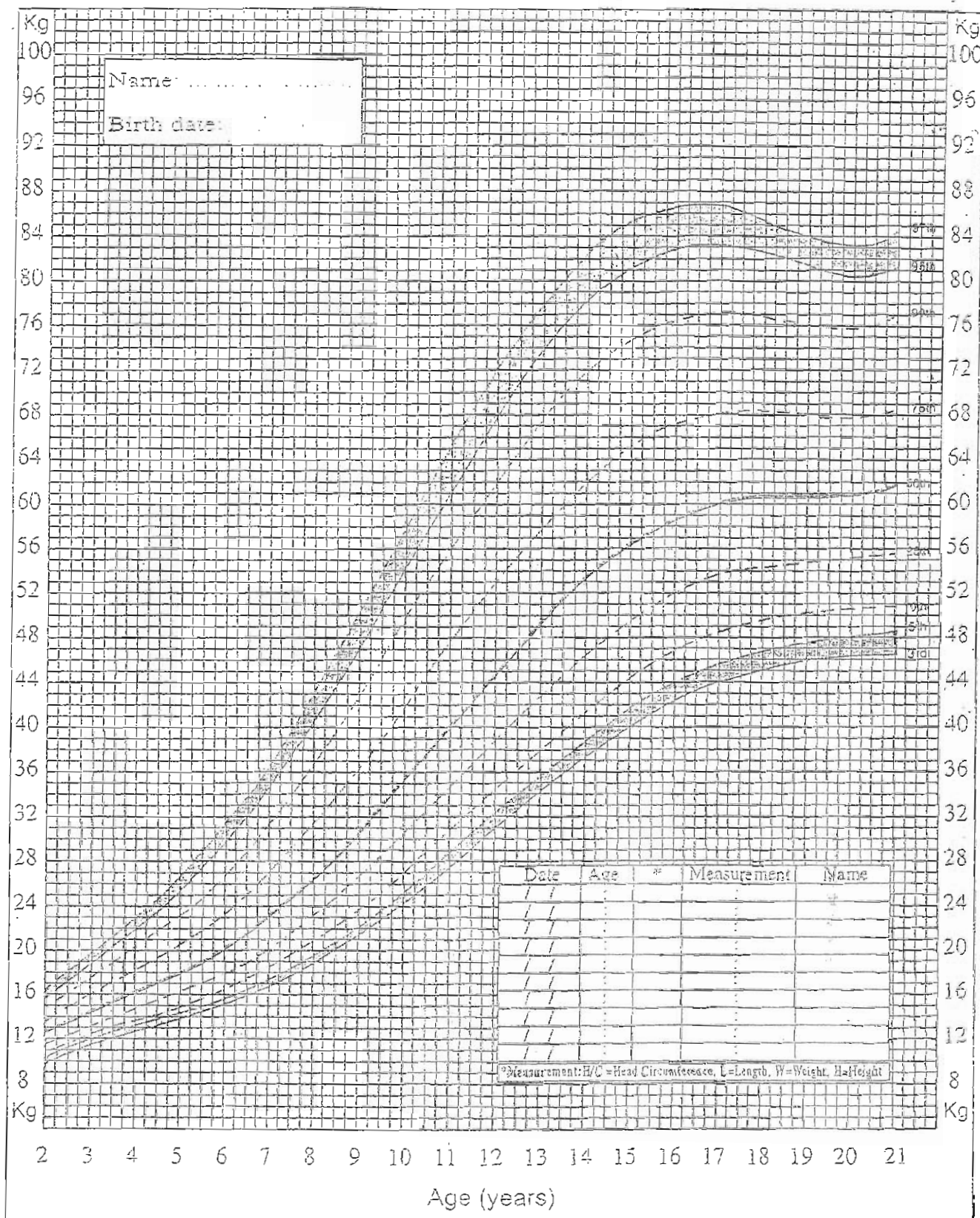
97th	174
95th	170
90th	166
75th	162
50th	158
25th	154
10th	150
5th	146
3rd	142

#### Acknowledgments:

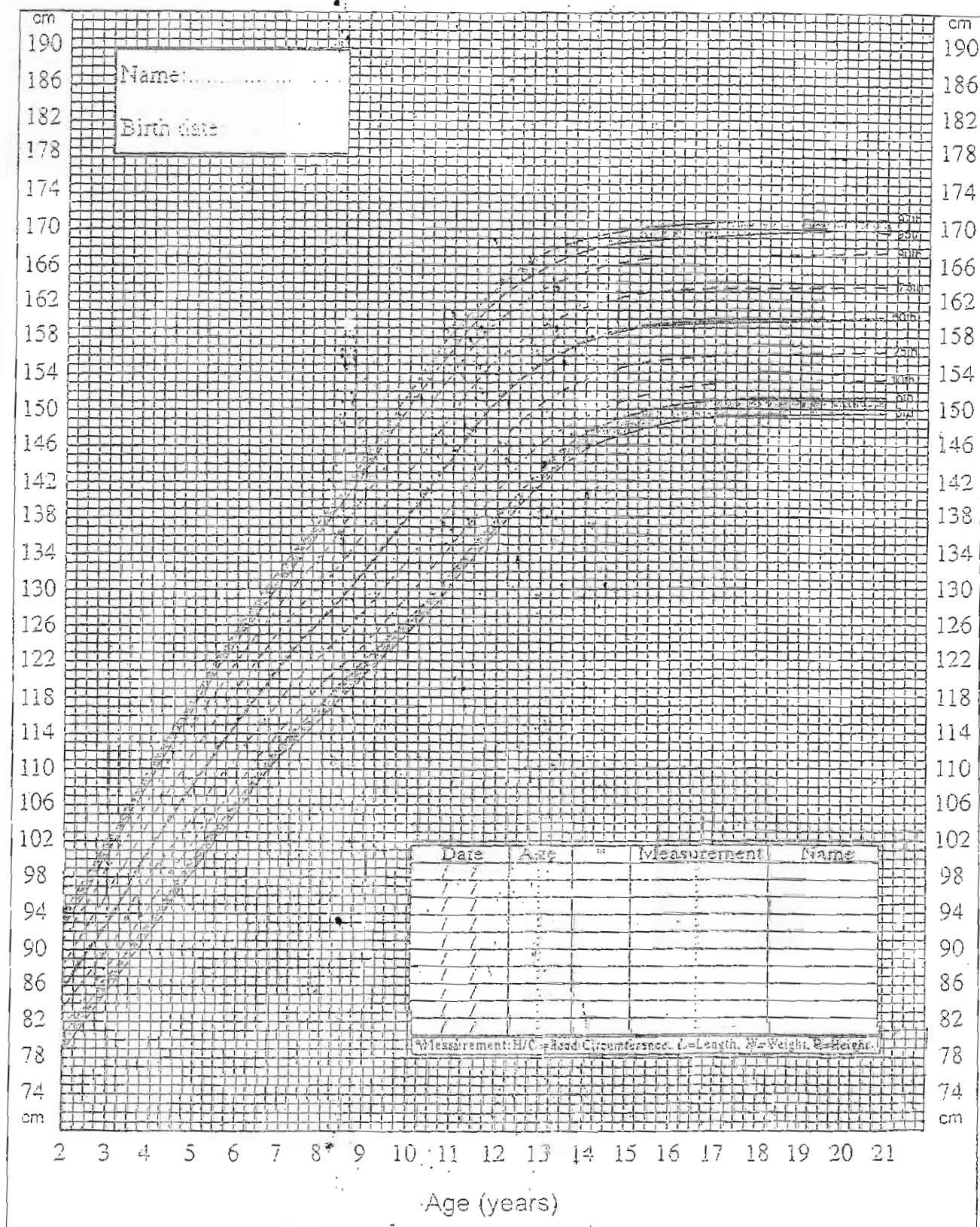
The Egyptian Supreme Council of Universities, Foreign Relations Coordination Unit (FRCU) - Mendez England & Associates, Cairo - The Egyptian Ministry of Education - The Egyptian Participating Schools and Universities.

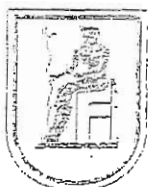
Diabetes, Endocrine and metabolism Pediatric Unit (D.E.M.P.U)

# Weight-for-Age Percentiles Egyptian Girls, 2 to 21 Years



# Stature-for-Age Percentiles: Egyptian Girls, 2 to 21 Years





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Faculty of Medicine

# GIRLS

## Egyptian Growth Charts, 2002 (Birth - 36 months)



جامعة القاهرة  
Cairo University

**Source:** Cairo University, Diabetic Endocrine and Metabolic Pediatric Unit and the National Research Centre - Cairo, in collaboration with Wright State University, School of Medicine, Department of Community Health Lifespan, Health Research Center. From a sample size of 33189 boys & girls (birth - 21 years):

- 2735 girls, for head circumference from birth - 36 months
- 2770 girls, for recumbent length from birth - 36 months
- 3016 girls, for weight from birth - 36 months
- 2602 girls, for weight for recumbent length from birth - 36 months

### How to measure:

**Weight:** from birth - 2 years, a girl should always be weighed naked on an appropriate self-calibrating or regularly calibrated scale. An older child should be weighed with her underwears. Record to the nearest 0.1 kg.

**Head circumference:** head circumference measurement should be taken from midway between the eyebrows and the hairline at the front of the head and the occipital prominence at the back. Appropriate thin plastic tape should be used.

**Supine length:** from birth to 2-3 years, a girl should be measured on her back by 2 people with appropriate equipment featuring a headboard and moveable footboard. Whilst one person holds the head against the headboard, with the head facing upwards in the Frankfurt plane\*, a second person measures the length by bringing the footboard up to the heels. Ensure that the legs are flat at the knee joints.

**Standing height:** from approximately 2-3 years onwards, standing height should be measured against an appropriate vertical measure. The heels should be together with the buttocks and shoulder blades touching the vertical and the head positioned in the Frankfurt plane\*. To ensure that the true height is taken, apply gentle upward pressure to the mastoid processes.

Record head circumference, length and height to the nearest 0.1 cm.

### How to Calculate the Target Centile Range (TCR):

From age 2 years onwards, if every girl follows her genetic growth pattern, she would be growing within her Target Centile Range (TCR) parallel to one of the centile lines. If not, refer to specialist. To calculate her TCR, apply the following steps: measure father's and mother's heights (a & b), calculate the sum (c), their mean height (d), the corrected Mid-Parental Height (MPH) (e) and the Target Centile Range (f) as shown. Apply arrow (e) opposite the corrected MPH, and draw vertical line above and below, opposite the TCR.

### Guidelines for recording, plotting and referral:

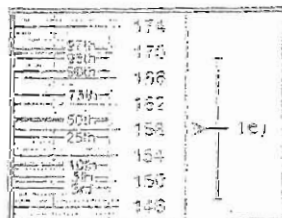
Record the measurements using the boxes included in this chart. Enter the date and current age. Specify the measurement in the box below the asterisk (i.e. H/C = Head circumference, H = Height, L = Length, W = Weight, W/L = Weight for length) and put your name. Plot each measurement on the curve with a well defined dot. Place the growth curve with a line but leave the dots clearly visible. A normal growth curve is one that always runs roughly on, or parallel to one of the printed centile lines. If it doesn't, consider these guidelines:

Refer a girl whose height falls above the 97<sup>th</sup> or below the 3<sup>rd</sup> centile line or outside her Target Centile Range (TCR). Refer her also, if her growth curve deviates upwards or downwards, over a period of 12-18 months, by a width of one centile distance.

In short-term undernutrition, weight declines before length, so values of weight for age and weight for recumbent length centiles are low compared to length for age centile. In long-term undernutrition, stunting is eventual, so in addition to the low weight for age centile, the length for age centile starts to deviate, whereas the weight for recumbent length centile returns towards normal. When weight falls below the 3<sup>rd</sup> centile, it is of value to determine the degree of malnutrition (look to the opposite table), this by expressing the patient weight as a percentage of the mean value of her age.

- a = Father's height
- b = Mother's height
- c = Sum of (a) and (b)
- d = (c) ÷ 2
- e = (d) - 7 cm = (MPH)
- f = MPH ± 11 cm

(a) =	174 cm
(b) =	156 cm
(c) =	330 cm
(d) =	165 cm
(e) =	165 - 7 = 158 cm
(f) =	158 ± 11 cm



Date	Age	*	Measurement	Name
14/03/03	9/12	L	72.5 cm	
14/03/03	9/12	H/C	46.0 cm	
14/03/03	9/12	W	9.3 kg	
14/03/03	9/12	W/L	75 th	

### Severity of Malnutrition

Grade of malnutrition	Weight for age*	Weight for length**
0, normal	> 90	> 90
1, mild	75 - 90	81 - 90
2, moderate	50 - 75	70 - 80
3, severe	< 50	< 70

\* Data from Gomez F, Cohen ZR, Frank S, et al. Mortality in second and third degree malnutrition. Trop Pediatr 2007; 145:10.

\*\* Data from Waterlow JC. Classification and definition of protein-calorie malnutrition. Br med J 3:366, 1972.

### Acknowledgments:

Egyptian Supreme Council of Universities, Foreign Relations Coordination Unit (FRCU) - Mendez England & Associates, Cairo - The Egyptian Ministry of Education - The Egyptian Participating Schools and Universities

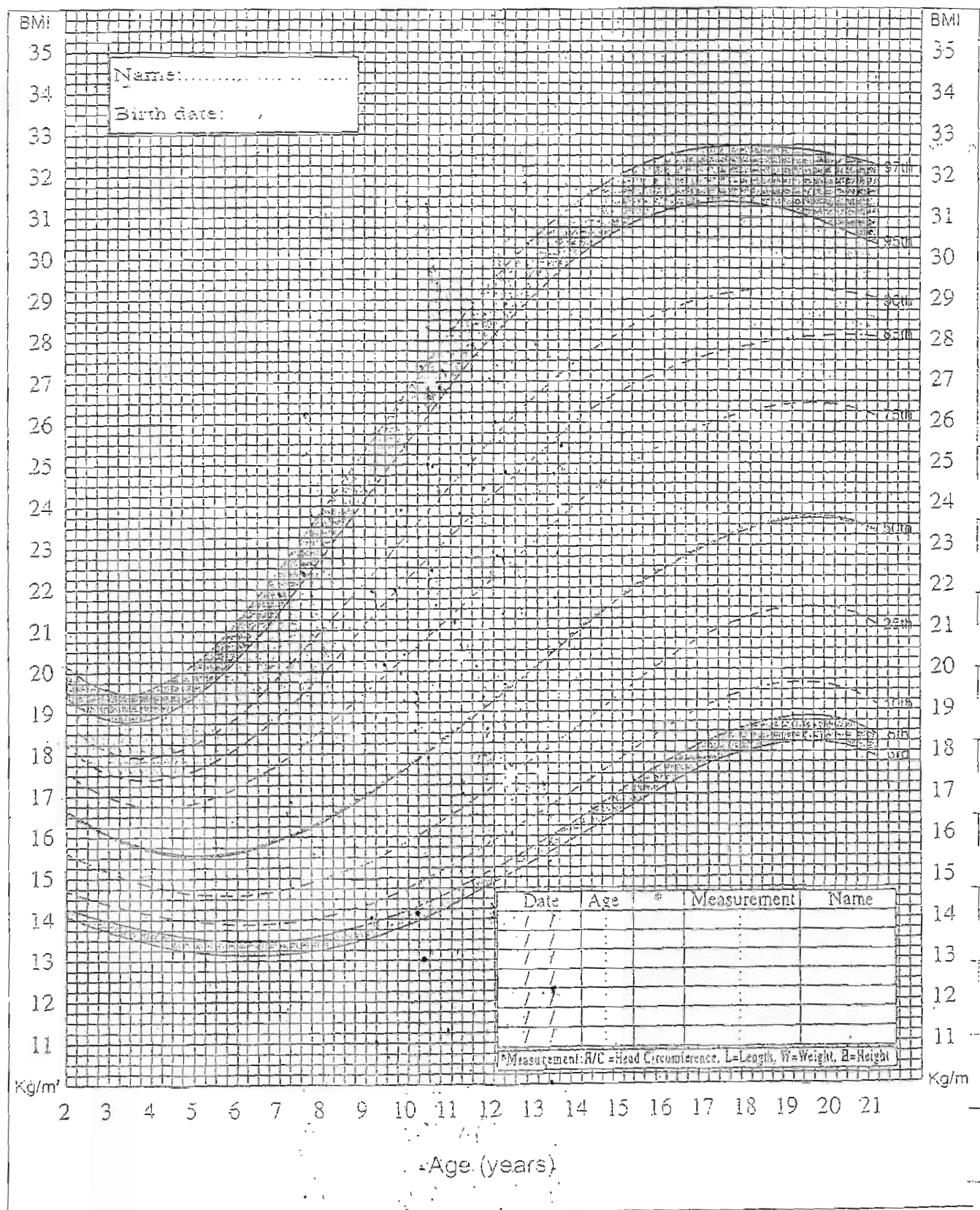
**Somatropin**  
Somatotropine 4IU

SEDICO pharmaceutical Company  
6 October City-Egypt  
www.sedico.net





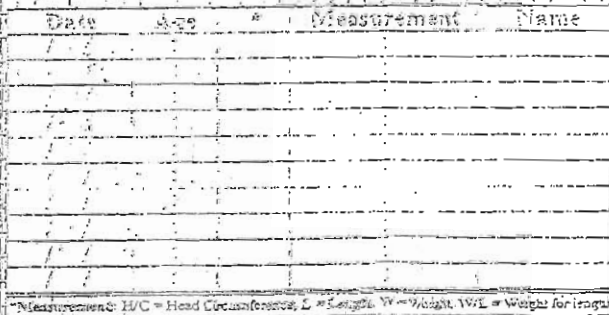
# Body Mass Index-for-Age Percentiles Egyptian Girls, 2 to 21 years



Price : 2.5 L.E











كلية الطب  
Faculty of Medicine

# BOYS

## Egyptian Growth Charts 2002

### (Birth - 36 months)



جامعة القاهرة  
Cairo University

**Source:** Cairo University, Diabetic Endocrine and Metabolic Pediatric Unit and the National Research Centre - Cairo, in collaboration with Wright State University, School of Medicine, Department of Community Health Lifespan, Health Research Center. From a sample size of 33189 boys & girls (birth - 21 years):

- 3100 boys, for head circumference from birth - 36 months.
- 3302 boys, for recumbent length from birth - 36 months.
- 6100 boys, for weight from birth - 36 months
- 0100 boys, for weight for recumbent length from birth - 36 months

#### How to measure:

**Weight:** from birth - 2 years, a boy should always be weighed naked on an appropriate, self-calibrating or regularly calibrated scale. An older boy should be weighed with his underwears. Record to the nearest 0.1 kg.

**Head circumference:** head circumference measurement should be taken from midway between the eyebrows and the hairline at the front of the head and the occipital prominence at the back. Appropriate thin plastic tape should be used.

**Recumbent length:** from birth to 2-3 years, a boy should be measured on his back by 2 people with appropriate equipment featuring a headboard and moveable footboard. Whilst one person holds the head against the headboard, with the head facing upwards in the Frankfurt plane\*, a second person measures the length by bringing the footboard up to the heels. Ensure that the legs are flat at the knee joints.

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The Frankfurt plane is an imaginary line from the center of the ear hole to the lower border of the eye socket.

#### How to Calculate the Target Centile Range (TCR):

From age 2 years onwards, if every boy follows his genetic growth pattern, he should be growing within his Target Centile Range (TCR) parallel to one of the centile lines. If not, refer to specialist. To calculate his TCR, apply the following steps: measure father's and mother's heights (a & b), calculate the sum (c), their mean height (d), the corrected Mid-Parental Height (MPH) (e) and the Target Centile Range (f) as shown. Apply arrow (e) opposite the corrected MPH, and draw a vertical line above and below, opposite the TCR.

#### Guidelines for recording, plotting and referral:

Record the measurements using the boxes included in this chart. Enter the date and the current age, specify the measurement in the box below the asterisk (i.e. H/C = Head circumference, H = Height, L = Length, W = Weight, W/L = Weight for length) and put your name. Plot each measurement on the curve with a well defined dot. Trace the growth curve with a line but leave the dots clearly visible. A normal growth curve is one that always runs roughly on, or parallel to one of the printed centile lines. If it doesn't, consider these guidelines:

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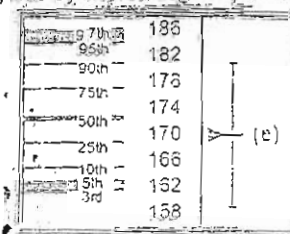
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- (c) = Sum of (a) and (b)
- (d) = (c) ÷ 2
- (e) = (d) + 7 cm = (MPH)
- (f) = MPH ± 12 cm

(a) =	174 cm
(b) =	156 cm
(c) =	330 cm
(d) =	165 cm
(e) =	165 + 7 = 172 cm
(f) =	172 ± 12 cm

Date	Age	*	Measurement	Name
14/03/03	9/12	L	72.5 cm	
14/03/03	9/12	H/C	46.0 cm	
14/03/03	9/12	W	9.3 Kg	
14/03/03	9/12	W/L	75 th	

Severity of Malnutrition		
Grade of malnutrition	Weight for age*	Weight for length**
0, normal	> 90	> 90
1, mild	75 - 90	81 - 90
2, moderate	60 - 74	70 - 80
3, severe	< 60	< 70

\* Data from Gomez F, Galvan RR, Frank S, et al. Mortality in second and third degree malnutrition. J Trop Pediatr 2:77, 1956  
\*\* Data from Waterlow JC: Classification and definition of protein-calorie malnutrition. Br Med J 3:566, 1972



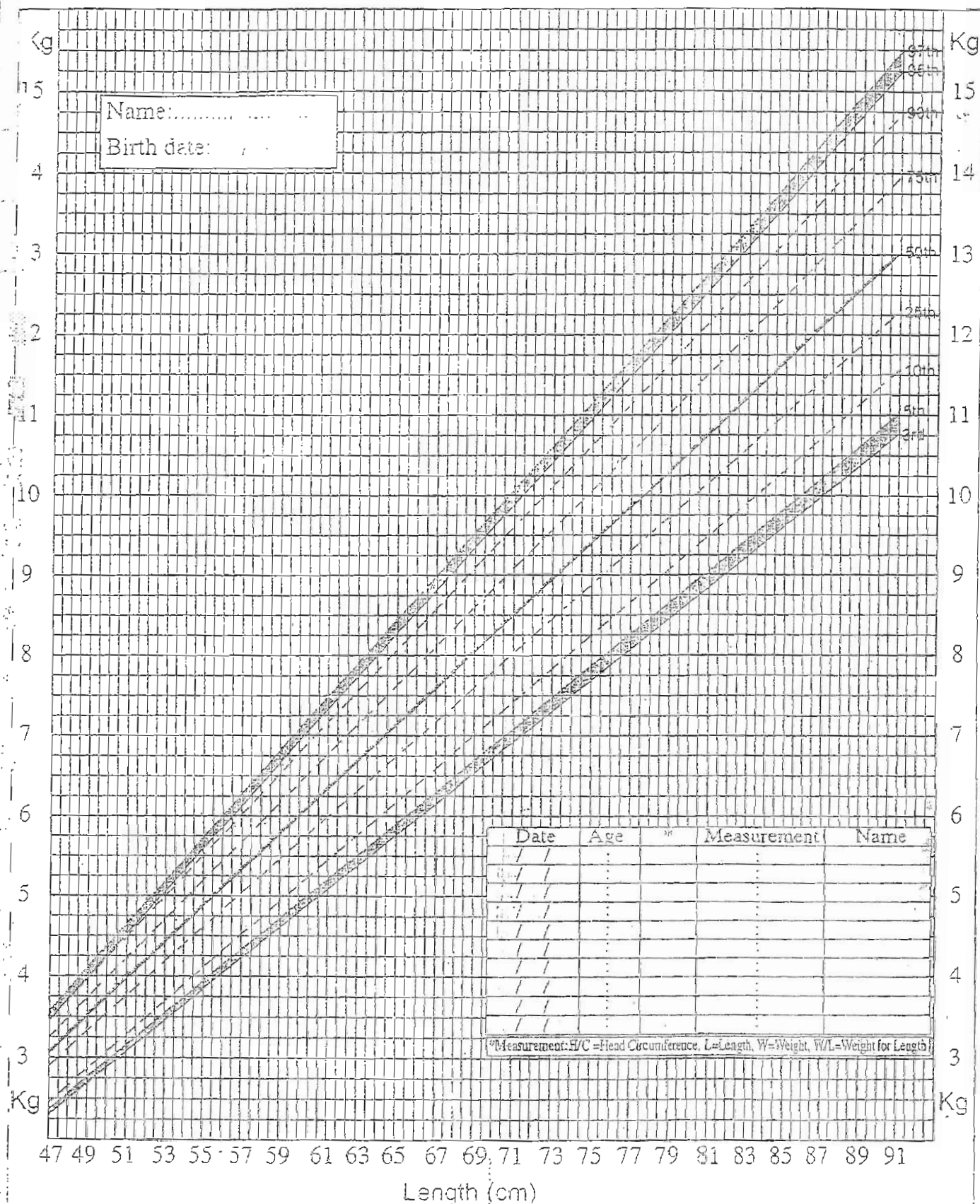
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Diabetes, Endocrine and metabolism, Pediatric Unit (D.E.M.P.U)



### Weight-for-Recumbent Length Percentiles: Egyptian Boys, Birth to 36 Months



Price : 2.5 L.E

White Knight Love

# Weight-for-Age Percentiles: Egyptian Boys, Birth to 36 Months

Name

Birth date:

Date	Age	*	Measurement	Name
/ /				
/ /				
/ /				
/ /				
/ /				
/ /				
/ /				
/ /				
/ /				
/ /				

\*Measurement: H/C=Head Circumference, L=Length, W=Weight, W/L=Weight for Length

Kg  
21  
20  
19  
18  
17  
16  
15  
14  
13  
12  
11  
10  
9  
8  
7  
6  
5  
4  
3  
2  
Kg

2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36  
Age (months)





Gas

## Pediatric Department Communication Skills Checklist

Student Name

Student No.

YES NO

### Initiating the session

- 1) Greet / Introduce self and role
- 2) Use names of family and child
- 3) Incorporate social talk at beginning of interview
- 4) Demonstrate respect, interest and attention

### Main Interview

- 5) Establish and use eye contact
- 6) Allow family (parent) sufficient time to speak
- 7) Move appropriately from open to closed questions
- 8) Listen actively and attentively
- 9) Facilitate responses verbally and non-verbally
- 10) Clarify statements
- 11) Demonstrate empathy and support
- 12) Acknowledge concerns, fears and feelings of patient and family
- 13) Use age-appropriate interview questions and techniques
- 14) Appear confident
- 15) Give clear information ( simple language, no jargon )
- 16) Give accurate and correct scientific information

### Closing the session

- 17) Encourage additional questions
- 18) Check understanding
- 19) Summarize and make follow up plan
- 20) Give a pleasant thank you and goodbye

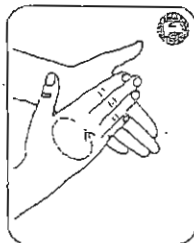
Babies on the Neonatal Unit are very young and their immune systems very immature. This makes them extremely susceptible to infection.

By washing your hands thoroughly you can remove bacteria, which may be harmful to your baby.

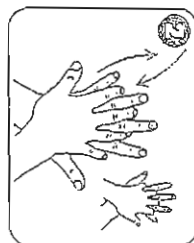
Yes—follow these steps to effectively wash your hands:

1. Take off your outdoor jacket or coat and hang it on the hooks provided (keep your valuables with you).
2. Roll up your sleeves and remove your watch, bracelets and rings. Keep them securely in your pocket or bag until you leave the Neonatal Unit.
3. Wet your hands.
4. Apply soap from the dispenser and wash your hands, wrists and lower arms following the instructions in the next panel.
5. Dry your hands, wrists and lower arms using the paper towels provided.
6. Finally, apply the alcohol provided in the dispenser, using the same technique as when washing your hands. It will dry in a few seconds.

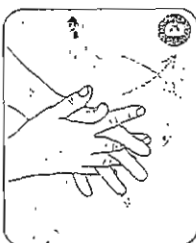
Follow this technique when washing your hands with soap and water and using alcohol gel.



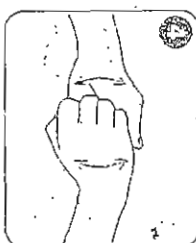
Rub soap and water or alcohol gel into your hands: palm to palm



Rub back of each hand with the palm of the other hand with fingers interlaced



Rub palm to palm with fingers interlaced



Rub with backs of fingers to opposing palms with fingers interlaced



Rub each thumb clasped in opposite hand using rotational movement



Rub tips of fingers in opposite palm in a circular motion



Rub each wrist with the opposite hand.

White Knight Love

White Knight Love

- Every time you go into the Neonatal Unit, this will help to reduce germs being carried into the unit from outside.

- In the nursery:

- before and after you touch or handle your baby
- after every nappy change
- before and after expressing breast milk
- before and after preparing the feed for your baby

- Each time you leave the nursery.

- Before you leave the Neonatal Unit. This helps to prevent germs being carried out of the unit.

If you have just washed your hands on leaving the nursery, you may use the alcohol gel instead of washing your hands before you leave the unit.

To help protect the babies on the Neonatal Unit, all parents and visitors are asked to follow the handwashing policy at all times.

We reserve the right to refuse entry to the Neonatal Unit if visitors do not follow the handwashing policy.

Please inform the Sister in Charge if you see anyone not following the handwashing policy.

If you or your relatives would like further information or advice about handwashing techniques, please speak to a member of staff.

*Good luck*

# Neonatology

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Early discharge (<48 hr) or very early discharge (<24 hr) may increase the risk of rehospitalization for hyperbilirubinemia, sepsis, failure to thrive, dehydration, and missed congenital anomalies.

## Recommendations for Early Discharge from the Normal Newborn Nursery

Uncomplicated antepartum, intrapartum, postpartum courses

Vaginal delivery

Singleton at 38–42 wk: appropriate for gestational age

Normal vital signs including respiratory rate < 60 breaths/min; axillary temperature 36.1–37°C (97.0–98.6°F) in open crib

Physical examination reveals no abnormalities requiring immediate attention

Urination; stool × 1

At least two uneventful, successful feedings

No excessive bleeding after (2 hr) circumcision

No jaundice within 24 hr of birth

Evidence of parental knowledge, ability, and confidence to care for the baby at home

Feeding

Cord, skin, genital care

Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)

Infant safety (car seat, supine sleep position, etc.)

Availability of family and physician support (physician follow-up)

Laboratory evaluation

Venereal Disease Research Laboratories (VDRL)

Hepatitis B surface antigen and vaccination or appointment for vaccination

State screening (e.g., phenylketonuria, thyroid, galactosemia, sickle cell)

Coombs' test

No social risks

Substance abuse

History of child abuse

Domestic violence

Mental illness

Teen mother

Homeless

## Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Week's Gestation.

### Major risk factors

1. PredischARGE TSB or TcB level in the high-risk zone.
2. Jaundice observed in the first 24 hr
3. Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (G6PD deficiency), elevated ETCO<sub>c</sub>
4. Gestational age 35–36 wk.
5. Previous sibling received phototherapy.
6. Cephalohematoma or significant bruising.
7. Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.
8. East Asian race.

### Minor risk factors

1. PredischARGE TSB or TcB level in the high intermediate-risk zone.
2. Gestational age 37–38 wk.
3. Jaundice observed before discharge.
4. Previous sibling with jaundice.
5. Macrosomic infant of a diabetic mother.
6. Maternal age  $\geq 25$  yr.
7. Male gender.

Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance).

1. TSB or TcB level in the low-risk zone
2. Gestational age  $\geq 41$  wk
3. Exclusive bottle feeding
4. Black race
5. Discharge from hospital after 72 hr

ETCO<sub>c</sub>, end tidal carbon monoxide; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

## Disorders of The Umbilicus

Anatomy: The cord contains:

- Two umbilical arteries.
- One vein.
- Rudimentary allantois.
- Remnant of the omphalomesenteric duct.
- Gelatinous substance called Wharton jelly.

### Types of abnormalities

1. Abnormally short cords are associated with (fetal hypotonia, oligohydramnios, uterine constraint)
2. Long cords (>70 cm) increase risk for true knots, wrapping around fetal parts (neck, arm) or prolapse, and fetal distress.
3. The umbilical cord usually sloughs within 2 wk. Delayed separation of the cord associated with neutrophil chemotactic defects.
4. A single umbilical artery: Trisomy 18 is one of the more frequent abnormalities.
5. Patency of the omphalomesenteric (vitelline) duct may be responsible for intestinal obstruction, intestinal fistula with fecal or bilious draining, prolapse of the bowel, a polyp (cyst), or a Meckel diverticulum. Therapy is surgical excision of the anomaly.
6. A persistent urachus is due to failure of closure of the allantoic duct and is associated with bladder outlet obstruction. Therapy is surgical excision.
7. CONGENITAL OMPHALOCELE.
8. TUMORS. Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst or myxosarcoma.
9. HEMORRHAGE due to trauma, inadequate ligation of the cord, or failure of normal thrombus formation or HDNB, septicemia, or local infection.
10. GRANULOMA. Persistence of granulation tissue at the base of the umbilicus is common. Treatment is cauterization with silver nitrate.
11. Umbilical polyp is bright red, and has a mucoid secretion. Treatment is surgical excision of the entire omphalomesenteric or urachal remnant.

## Differential Diagnosis of Cyanosis in the Newborn

### 1. Central or peripheral nervous system hypoventilation

Birth asphyxia  
Intracranial hypertension, hemorrhage  
Oversedation (direct or through maternal route)  
Diaphragm palsy  
Neuromuscular diseases  
Seizures

### 2. Respiratory disease

Upper airway  
Choanal atresia/stenosis  
Pierre Robin syndrome  
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)  
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)  
Lower airway  
Respiratory distress syndrome  
Transient tachypnea  
Meconium aspiration  
Pneumonia (sepsis)  
Pneumothorax  
Congenital diaphragmatic hernia  
Pulmonary hypoplasia

### 3. Cardiac right-to-left shunt

Abnormal connections (pulmonary blood flow normal or increased)  
Transposition of great vessels  
Total anomalous pulmonary venous return  
Truncus arteriosus  
Hypoplastic left heart syndrome  
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis  
Obstructed pulmonary blood flow (pulmonary blood flow decreased)  
Pulmonic atresia with intact ventricular septum  
Tetralogy of Fallot  
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect

## Classification of Hypoglycemia in Infants and Children

### NEONATAL TRANSIENT HYPOGLYCEMIA

Associated with inadequate substrate or immature enzyme function in otherwise normal neonates

Prematurity

Small for gestational age

Transient neonatal hyperinsulinism also present in:

Infant of diabetic mother

Birth asphyxia

Infant of toxemic mother

### NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS

#### Hormonal disorders

Hyperinsulinism

K<sub>ATP</sub> channel H1 mutations

Hyperinsulinism/hyperammonemia syndrome

Acquired islet adenoma

Beckwith-Wiedemann syndrome

Insulin administration (Munchausen syndrome by proxy)

Oral sulfonylurea drugs

Congenital disorders of glycosylation

Counter-regulatory hormone deficiency

Panhypopituitarism

Isolated growth hormone deficiency

Adrenocorticotrophic hormone deficiency

Addison disease

#### Glycogenolysis and gluconeogenesis disorders

Fructose-1,6-diphosphatase deficiency

Pyruvate carboxylase deficiency

Galactosemia

Hereditary fructose intolerance

Glycogen storage disease



## Transfusion Protocol for new born

Hct/Hgb	RESPIRATORY SUPPORT AND/OR SYMPTOMS	TRANSFUSION VOLUME
Hct $\leq$ 35/ Hgb $\leq$ 11	Infants requiring moderate or significant mechanical ventilation (MAP $>$ 8 cm H <sub>2</sub> O and FIO <sub>2</sub> $>$ 0.4)	15 mL/kg PRBCs <sup>141</sup> over period of 2–4 hr
Hct $\leq$ 30/ Hgb $\leq$ 10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal CPAP $>$ 6 cm H <sub>2</sub> O and FIO <sub>2</sub> $\leq$ 0.4)	15 mL/kg PRBCs over period of 2–4 hr
Hct $\leq$ 25/ Hgb $\leq$ 8	Infants not requiring mechanical ventilation but who are receiving supplemental O <sub>2</sub> or CPAP with an FIO <sub>2</sub> $\leq$ 0.4 and in whom 1 or more of the following is present: <ul style="list-style-type: none"> <li>• <math>\leq</math> 24 hr of tachycardia (HR <math>&gt;</math> 180) or tachypnea (RR <math>&gt;</math> 80)</li> <li>• An increased oxygen requirement from the previous 48 hr, defined as a <math>\geq</math> 4-fold increase in nasal cannula flow (i.e., 0.25 to 1 L/min) or an increase in nasal CPAP <math>\geq</math> 20% from the previous 48 hr (i.e., 5 to 6 cm H<sub>2</sub>O)</li> <li>• Weight gain <math>&lt;</math> 10 g/kg/day over the previous 4 days while receiving <math>\geq</math> 100 kcal/kg/day</li> <li>• An increase in episodes of apnea and bradycardia (<math>&gt;</math> 9 episodes in a 24-hr period or <math>\geq</math> 2 episodes in 24 hr requiring bag and mask ventilation) while receiving therapeutic doses of methylxanthines</li> <li>• Undergoing surgery</li> </ul>	20 mL/kg PRBCs over period of 2–4 hr (divide into 2–10 mL/kg volumes if fluid sensitive)
Hct $\leq$ 20/ Hgb $\leq$ 7	Asymptomatic and an absolute reticulocyte count $<$ 100,000 cells/ $\mu$ L	20 mL/kg PRBCs over period of 2–4 hr (2–10 mL/kg volumes)

# Nosocomial infection

## *Definition*

Nosocomial (hospital-acquired) defined as any infection occurring after admission to the NICU that was not transplacentally acquired. It occurs after 30 days of birth.

## *Risk factors*

1. Prematurity
2. LBW
3. Invasive procedures
4. Indwelling vascular catheters
5. Parenteral nutrition with lipid emulsions
6. Endotracheal tubes
7. Ventricular shunts
8. Alterations in the skin and/or mucous membrane barriers
9. Frequent use of broad-spectrum antibiotics
10. Prolonged hospital stay

*Sequels* : serious infections as pneumonia, meningitis, omphalitis, and necrotizing enterocolitis, sepsis and DIC .

## *Mode of transmission :*

direct contact or indirectly via contaminated equipment, intravenous fluids, medications, blood products, or enteral feedings.

## *Pathogenesis:*

Colonization of the infant's skin, umbilicus, and respiratory or gastrointestinal tract with pathogenic agents often precedes the development of infection.

Antibiotic use interferes with colonization by normal flora, thereby facilitating colonization with more virulent pathogens.

## *Etiology*

### a) Gram-positive organisms

- Staphylococcus—coagulase negative
- Staphylococcus aureus(MRSA) .
- Enterococcus spp.
- Group B streptococci

## PREVENTION OF NOSOCOMIAL INFECTION

1. Observe recommendations for universal precautions with all patient contact
  - o Gloves
  - o Gowns, mask, and isolation as indicated
2. Nursery design engineering
  - Appropriate nursing: patient ratio
  - Avoid overcrowding and excessive workload
  - Readily accessible sinks, antiseptic solutions, soap, and paper towels
3. Handwashing
  - o Improve handwashing compliance
  - o Wash hands before and after each patient encounter
  - o Appropriate use of soap, alcohol-based preparations, or antiseptic solutions
  - o Alcohol-based antiseptic solution at each patient bedside
  - o Provide emollients for nursery staff
  - o Education and feedback for nursery staff
4. Minimizing risk of CVC contamination
  - Maximal sterile barrier precautions during CVC insertion
  - Local antiseptics with chlorhexidine gluconate
  - Minimize repeated entry into the line for laboratory tests
  - Aseptic technique when entering the line
  - Minimize CVC days
  - Sterile preparation of all fluids to be administered via a CVC
5. Meticulous skin care
6. Encourage early and appropriate advancement of enteral feeding
7. Education and feedback for nursery personnel
8. Continuous monitoring and surveillance of nosocomial infection rates in the NICU

# Fetal and Neonatal Infection

A number of agents may infect newborns in utero, intrapartum, or postpartum.

- A. Intrauterine transplacental : (Syphilis, rubella, CMV, toxoplasmosis, parvovirus B19, and varicella).
- B. Intrapartum and/or transplacental infection: HSV, HIV, hepatitis B virus (HBV), hepatitis C virus, and tuberculosis (TB).

## Neonatal Infection by Age of Onset

CHARACTERISTICS	EARLY ONSET	LATE ONSET
Age at onset	Birth to 7 days usually <72 hr	7 to 30 days
Maternal obstetric complications	Common	Uncommon
Prematurity	Frequent	Varies
Organism source	Maternal genital tract	Maternal genital tract/environment
Manifestation	Multisystem	Multisystem or focal
Site	Normal nursery, NICU, community	NICU, community

## Bacterial Causes of Systemic Neonatal Infections

### BACTERIA

#### Gram positive(early onset)

Clostridia  
 Enterococci  
 Group B streptococcus  
*Listeria monocytogenes*  
 Other streptococci  
*Staphylococcus aureus*  
 Staphylococcus, coagulase negative  
*Streptococcus pneumoniae*  
 Viridans streptococcus

#### Gram negative

Bacteroides  
*Campylobacter/citrobacter/enterobacter*  
*Escherichia coli*  
*Haemophilus influenzae*  
*Klebsiella*  
*Neisseria gonorrhoeae*  
*Neisseria meningitidis*  
*Proteus*  
*Pseudomonas*  
*Salmonella(late onset)*

#### Others

*Treponema pallidum*  
*Mycobacterium tuberculosis*

## Initial Signs and Symptoms of Infection in Newborn Infants

### GENERAL

- Fever, temperature instability
- "Not doing well"
- Poor feeding
- Edema

### GASTROINTESTINAL SYSTEM (No GE in newborn, sepsis or no sepsis)

- Abdominal distention
- Vomiting
- Diarrhea
- Hepatomegaly

### RESPIRATORY SYSTEM

- Apnea, dyspnea
- Tachypnea, retractions
- Flaring, grunting
- Cyanosis

### RENAL SYSTEM

- Oliguria.

### CARDIOVASCULAR SYSTEM

- Pallor, mottling; cold, clammy skin
- Tachycardia
- Hypotension
- Bradycardia

### CENTRAL NERVOUS SYSTEM

- Irritability, lethargy
- Tremors, seizures
- Hyporeflexia, hypotonia
- Abnormal Moro reflex

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## Manifestations of Neonatal Bacterial Infections

### Abdomen

Peritonitis  
Hepatitis  
Adrenal abscess  
Gallbladder hydrops

### Brain

Meningitis  
Abscess  
Subdural empyema  
Cerebritis  
Ventriculitis

### CVS

Endocarditis  
Pericarditis  
Myocarditis

### Ocular

Conjunctivitis  
Chorioretinitis

### Osteoarticular

Arthritis  
Osteomyelitis  
Dactylitis

### Respiratory tract

Pneumonia  
Otitis media  
Mastoiditis  
Retropharyngeal cellulitis  
Empyema

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# Neonatal sepsis

## Early-onset neonatal sepsis

The microorganisms most commonly associated with early-onset neonatal sepsis include the following:

- GBS
- E coli
- Coagulase-negative Staphylococcus
- H influenzae
- L monocytogenes

## Risk factors:

- Maternal GBS colonization (especially if untreated during labor)
- Premature rupture of membranes (PROM)
- Prematurity
- Maternal urinary tract infection
- Chorioamnionitis
- Low Apgar score (< 6 at 1 or 5 minutes)
- Maternal fever greater than 38°C
- Maternal urinary tract infection (UTI)
- Poor prenatal care
- Poor maternal nutrition
- Low socioeconomic status
- Low birth weight

## Late-onset neonatal sepsis

Organisms that have been implicated in causing late-onset neonatal sepsis include the following:

- Coagulase-negative staphylococci
- S aureus
- E coli
- Klebsiella
- Pseudomonas
- Enterobacter
- Candida
- GBS
- Serratia
- Acinetobacter
- Anaerobes



### Clinical Criteria for the Diagnosis of Sepsis

1. Convulsions
2. Respiratory rate >60 breaths/min
3. Severe chest indrawing
4. Nasal flaring
5. Grunting
6. Bulging fontanel
7. Pus draining from the ear
8. Redness around umbilicus extending to the skin
9. Temperature > 37.7°C (or feels hot) or <35.5°C (or feels cold)
10. Lethargic or unconscious
11. Reduced movements
12. Not able to feed
13. Not attaching to the breast
14. No suckling at all
15. Crepitations
16. Cyanosis
17. Reduced digital capillary refill time

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## Evaluation of a Newborn for Infection or Sepsis

### I- HISTORY (SPECIFIC RISK FACTORS)

#### Maternal

Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy)

Urinary tract infection

Chorioamnionitis

Maternal colonization with GBS, *Neisseria gonorrhoeae*, herpes simplex

Gestational age/birthweight

Multiple birth

Duration of membrane rupture

Complicated delivery

#### Fetal

Fetal tachycardia (distress)

Age at onset (in utero, birth, early postnatal, late)

Location at onset (hospital, community)

Medical intervention

Vascular access

Endotracheal intubation

Parenteral nutrition

Surgery

### EVIDENCE OF OTHER DISEASES

Congenital malformations (heart disease, neural tube defect)

Respiratory tract disease (RDS, aspiration)

Necrotizing enterocolitis

Metabolic disease, e.g., galactosemia

### EVIDENCE OF FOCAL OR SYSTEMIC DISEASE:

General appearance, neurologic status

Abnormal vital signs

Organ system disease

Feeding, stools, urine output, extremity movement

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## Treatment

### Antimicrobial therapy

- ☐ Initial (empiric) therapy is most often begun before a definite causative agent is identified.
- ☐ Continuing therapy is based on culture and sensitivity results, clinical course & laboratory studies (e.g., CRP).

### Selection of the appropriate antimicrobial therapy

#### Early onset neonatal sepsis

- ☐ Obtain cultures first.
- ☐ Recommended 1st line antibiotics: ampicillin + gentamicin.
- ☐ Third generation cephalosporins (cefotaxime or ceftazidime) may be added to gentamicin, if meningitis is clinically suspected.

#### Late onset neonatal sepsis

- Staphylococcal coverage with vancomycin + aminoglycoside *or* 3rd-generation cephalosporin.
- Anaerobic infection: Clindamycin
- Fungal infection: Fluconazole or Amphotericin B
- Remove central catheters to eradicate infection.

### Duration of therapy

- ✓ Generally for 10-14 days.
- ✓ Meningitis, continue therapy for 14-21 days.

### Monitoring of therapy

- ☐ All infants receiving aminoglycosides and vancomycin must have serum concentrations monitored.
- ☐ Infants with shock or renal compromise should have serum levels monitored after the first dose.

### Supportive therapy

- ✦ Inotropic agents and volume support for hypotension and poor perfusion.
- ✦ Electrolytes correction.
- ✦ Enteral or parenteral nutrition, according to the needs.
- ✦ MV and/or exogenous surfactant for pneumonia and RDS.
- ✦ Sodium bicarbonate for metabolic acidosis.
- ✦ Anticonvulsants for seizures.

### Intravenous immunoglobulin (IVIG)

A single dose (500-750 mg/kg/dose over 2-6 hrs) for seriously ill infants with overwhelming sepsis is an adjunctive therapy.

# Transplacental infection

## Cytomegalovirus

### *Mode of transmission :*

- Contact through saliva, urine, and/or other body fluids.
- Sexual contact
- Organ transplantation
- Transplacental transmission
- Transmission via breast milk, and blood transfusion (rare).

### *Clinical manifestation :*

- ⊗ Intrauterine growth restriction
- ⊗ Sensorineural hearing loss
- ⊗ Intracranial calcifications
- ⊗ Microcephaly, hydrocephalus.
- ⊗ Hepatosplenomegaly
- ⊗ Delayed psychomotor development.
- ⊗ Chorioretinitis and Optic atrophy.
- ⊗ Thrombocytopenia

### **RISK OF INFECTION**

Severe sequelae are more common with infection in the first trimester, while the overall risk of infection is greatest in the third trimester.

## Herpes simplex virus

*Causative organisms :* HSV-1 and HSV-2 may cause neonatal herpes. HSV-2 is responsible for 70% of cases. Neonatal herpetic infection is defined as infection within 28 days of birth.

*Mode of transmission :* transplacentally or via an ascending infection from the cervix

### *Clinical manifestation:*

- Localized skin, eye, or mouth disease.
- Meningitis or encephalitis.
- Disseminated disease that involves multiple organs.
- Intrauterine infection is associated with intrauterine growth restriction, preterm labor, and miscarriage.

## Enterovirus

*Enterovirus infections caused by coxsackievirus and echovirus leads to:*

- Miscarriage.
- Neurodevelopmental delay and global cognitive defects.
- Myocarditis.
- Cortical necrosis.
- Respiratory failure.

## Measles virus

*Clinical manifestation*

- Spontaneous abortion.
- Premature labor.
- Low birth weight.
- Pneumonitis.
- Skin rash.

## Lymphocytic choriomeningitis virus

*Clinical manifestation*

- Chorioretinitis.
- Hydrocephalus .
- Mental retardation.
- Visual impairment.
- Intrauterine death is possible.

## HIV

*Clinical manifestations.*

- Asymptomatic, but may present with
- Lymphadenopathy and/or hepatosplenomegaly.
- Poor weight gain as might be found in chronic viral infection
- Neuromotor abnormalities or encephalopathy.

## Recommended Newborn Screening

### DISORDERS OF ORGANIC-ACID METABOLISM

Isovaleric acidemia  
 Glutaric aciduria type I  
 3-Hydroxy-3-methylglutaric aciduria  
 Multiple carboxylase deficiency  
 Methylmalonic acidemia, mutase deficiency form  
 3-Methylcrotonyl-CoA carboxylase deficiency  
 Methylmalonic acidemia, Cbl A and Cbl B-forms  
 Propionic acidemia  
 Beta-ketothiolase deficiency

### DISORDERS OF FATTY ACID METABOLISM

Medium-chain acyl-CoA dehydrogenase deficiency  
 Very long-chain acyl-CoA dehydrogenase deficiency  
 Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency  
 Trifunctional protein deficiency  
 Carnitine uptake defect

### DISORDERS OF AMINO-ACID METABOLISM

Phenylketonuria  
 Maple syrup urine disease  
 Homocystinuria  
 Citrullinemia  
 Argininosuccinic acidemia  
 Tyrosinemia type I

### HEMOGLOBINOPATHIES

Sickle cell anemia  
 Hemoglobin S- $\beta$ -thalassemia  
 Hemoglobin SC disease

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## Neonatal Seizures

### *Overview*

Generalized tonic-clonic convulsions tend not to occur in the 1st mo of life. The arborization of axons and dendritic processes as well as myelination is incomplete in the neonatal brain. A seizure discharge, therefore, cannot readily be propagated throughout the neonatal brain to produce a generalized seizure.

### ***CLINICAL MANIFESTATIONS AND CLASSIFICATION***

1. Focal seizures consist of rhythmic twitching of muscle groups. These seizures are often associated with localized structural lesions as well as with infections and subarachnoid hemorrhage.
2. Multifocal clonic convulsions are similar to focal clonic seizures but differ in that many muscle groups are involved, frequently several simultaneously.
3. Tonic seizures are characterized by rigid posturing of the extremities and trunk and are sometimes associated with fixed deviation of the eyes
4. Myoclonic seizures are brief focal or generalized jerks of the extremities or body that tend to involve distal muscle groups.
5. Subtle seizures consist of chewing motions, excessive salivation, and alterations in the respiratory rate including apnea, blinking, nystagmus, bicycling or pedaling movements, and changes in color.
6. Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd–3rd day of life, with a seizure frequency of 10–20/day. Patients are normal between seizures, which stop in 1–6 mo.
7. Fifth-day fits occur on day 5 of life (4–6 days) in normal-appearing neonates. The seizures are multifocal and are present for less than 24 hr. The prognosis is good.
8. Pyridoxine dependency: generalized clonic seizures which are resistant to conventional anticonvulsants, such as phenobarbital or phenytoin. Treatment: 100–200 mg or pyridoxal phosphate monitored by EEG, followed by 6 wk trial of oral pyridoxine (10–20 mg/day).
9. Drug withdrawal seizures due to barbiturates, benzodiazepines, heroin, and methadone.

# Causes of Neonatal Seizures

## AGES 1-4 DAYS

Hypoxic-ischemic encephalopathy  
 Drug toxicity or withdrawal  
 Intraventricular hemorrhage  
 Hypocalcemia  
 Sepsis  
 Hypoglycemia  
 Hypomagnesemia  
 Hyponatremia or hypernatremia  
 Inborn errors of metabolism

## AGES 4-14 DAYS

Infection  
 Meningitis, encephalitis  
 Hypocalcemia  
 Hypoglycemia, persistent  
 Inherited disorders of metabolism  
 Beckwith syndrome  
 Kernicterus, hyperbilirubinemia

## AGES 2-8 WEEKS

Infection  
 Encephalitis, bacterial meningitis  
 Head injury/ Subdural hematoma, child abuse  
 Inherited disorders of metabolism  
 Neonatal adrenoleukodystrophy  
 Cytoarchitectural abnormalities of the brain (including lissencephaly and schizencephaly)  
 Tuberous sclerosis  
 Sturge-Weber syndrome



## Factors Affecting the Apgar Score

### FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR)

- Immaturity
- Analgesics, narcotics, sedatives
- Magnesium sulfate
- Acute cerebral trauma
- Precipitous delivery
- Congenital myopathy
- Congenital neuropathy
- Spinal cord trauma
- Central nervous system anomaly
- Lung anomaly (diaphragmatic hernia)
- Airway obstruction (choanal atresia)
- Congenital pneumonia and sepsis
- Previous episodes of fetal asphyxia (recovered)
- Hemorrhage-hypovolemia

### FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR)

- Maternal acidosis
- High fetal catecholamine levels
- Some full-term infants

Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

## Common Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
1) Choanal atresia	Respiratory distress in delivery room, apnea, unable to pass nasogastric tube through nares. Suspect CHARGE syndrome
2) Pierre Robin syndrome	Micrognathia, cleft palate, airway obstruction
3) Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
4) Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, unable to place nasogastric tube in stomach. Suspect VATER syndrome
5) Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention. Suspect trisomy 21, cystic fibrosis, cocaine
6) Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
7) Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
8) Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated $\alpha$ -fetoprotein, decreased fetal activity
9) Ductal-dependent congenital heart disease	Cyanosis, hypotension, murmur

**CHARGE:** coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies;

**VATER:** vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

Clinical BIND score of onset, severity and progression of ABE in infants with hyperbilirubinemia (TSB >95th percentile for age in hours) as elicited by history and physical examination

Clinical signs	BIND score	ABE
<b>A. Mental status</b>		
▪ Normal	0	None
▪ Sleepy but arousable; decreased feeding	1	Subtle
▪ Lethargy, poor suck and/or irritable/jittery with strong suck	2	Moderate
▪ Semi-coma, apnea, unable to feed, seizures, coma	3	Advanced
<b>B. Muscle tone</b>		
▪ Normal	0	None
▪ Persistent mild to moderate hypotonia	1	Subtle
▪ Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2	Moderate
▪ Persistent retrocollis and opisthotonos—bicycling or twitching of hands and feet	3	Advanced
<b>C. Cry pattern</b>		
▪ Normal	0	None
▪ High pitched when aroused	1	Subtle
▪ Shrill, difficult to console	2	Moderate
▪ Inconsolable crying or cry weak or absent	3	Advanced
Total BIND score		
Nurse/MD signature		

Abbreviations: BIND, bilirubin-induced neurological dysfunction; ABE, acute bilirubin encephalopathy; TSB, total serum bilirubin.

- **Score of 7–9** represent advanced ABE: urgent, prompt and individualized intervention are recommended to prevent further brain damage, minimize severity of sequelae and possibly reverse acute damage.
- **Score of 4–6:** represent moderate ABE and are likely to be reversible with urgent and prompt bilirubin reduction strategies.
- **Score of 1–3:** are consistent with subtle signs of ABE in infants with hyperbilirubinemia. An abnormal ABR or 'referred' automated ABR is indicative of likely bilirubin neurotoxicity and would be suggestive of moderate ABE. In infants with these non-specific signs (score 1–3), a failed ABR hearing screen supports a diagnosis of moderate ABE.

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## **HYPERTHERMIA IN THE NEWBORN**

(TRANSITORY FEVER OF THE NEWBORN, DEHYDRATION FEVER)

### Causes:

1. Breast-fed infants whose intake of fluid has been particularly low (dehydration fever).
2. Infants who are overdressed.
3. Infants who are exposed to high environmental temperatures, either in an incubator, in a bassinette near a radiator, or in the sun.
4. Local or systemic infection.

### Clinical picture:

- The infant may lose weight.
- Dehydration (Urinary output and the frequency of voiding diminish)
- Increase in serum levels of protein and sodium and with an increase in hematocrit.
- The possibility of local or systemic infection should be evaluated.
- The skin is hot and dry, and initially the infant usually appears flushed and apathetic.
- Tachypnea and irritability may be noted.
- In advanced stage: stupor, grayish pallor, coma, and convulsions.
- Hyperthermia has been associated with sudden infant death and with hemorrhagic shock and encephalopathy syndrome.

### Treatment and prevention :

- ✦ Dressing infants in clothing suitable for the temperature of the immediate environment.
- ✦ Administering oral or parenteral fluids and correct any electrolytes disturbances
- ✦ Lowering the environmental temperature leads to prompt reduction of the fever and alleviation of symptoms.
- ✦ In newborn infants, exposure of the body to usual room temperature or immersion in tepid water usually suffices to bring the temperature back to normal levels.

## Diaphragmatic Hernia

**Definition:** A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax. The etiology may be congenital or traumatic.

**Types:** The defect may be at the

- a) Esophageal hiatus (hiatal).
- b) Paraesophageal (adjacent to the hiatus).
- c) Retrosternal (Morgagni).
- d) Posterolateral (Bochdalek) portion of the diaphragm (90% of cases)

**Pathogenesis:**

- ⇒ Pulmonary hypoplasia.
- ⇒ Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli with decreased levels of phosphatidylcholine, total DNA, and total lung protein.

### CLINICAL PRESENTATION

- ⊗ Respiratory distress is a cardinal sign in babies with CDH. This may occur immediately or there may be a "honeymoon" period of up to 48 hr when the baby is relatively stable.
- ⊗ The clinical signs of respiratory distress (tachypnea, grunting, use of accessory muscles, and cyanosis).
- ⊗ Children with CDH will also have a scaphoid abdomen and increased chest wall diameter.
- ⊗ Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally.
- ⊗ The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred.

### DIAGNOSIS

- CDH can be diagnosed on prenatal ultrasound (between 16 and 24 wk) in over 50% of cases.
- A chest x-ray and nasal gastric tube is all that is usually required to confirm the diagnosis.

**Treatment:**

1. Rapid endotracheal intubation, sedation, and possibly paralysis. A preductal  $\text{SaO}_2$  of 85% or greater should be the minimum goal.
2. Prolonged mask ventilation, which enlarges the stomach and small bowel thus making oxygenation more difficult, should be avoided.
3. **SURGICAL REPAIR.** Most centers will wait at least 48 hr after stabilization and resolution of the pulmonary hypertension.

### COMPLICATIONS

- ⊕ Bronchopulmonary dysplasia & gastroesophageal reflux disease (GERD).
- ⊕ Neurocognitive defects are common, pectus excavatum and scoliosis.

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*White Knight Love*

*Good luck*

# Hematology

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## Indications of blood & blood components transfusion

### Guidelines for Pediatric Red Blood Cell Transfusions

#### CHILDREN AND ADOLESCENTS

- Acute loss of >25% of circulating blood volume
- Hemoglobin of <8.0 g/dL<sup>†</sup> in the perioperative period
- Hemoglobin of <13.0 g/dL and *severe* cardiopulmonary disease
- Hemoglobin of <8.0 g/dL and *symptomatic* chronic anemia
- Hemoglobin of <8.0 g/dL and *marrow failure*

#### INFANTS WITHIN THE FIRST 4 MO OF LIFE

- Hemoglobin of <13.0 g/dL and *severe* pulmonary disease
- Hemoglobin of <10.0 g/dL and *moderate* pulmonary disease
- Hemoglobin of <13.0 g/dL and *severe* cardiac disease
- Hemoglobin of <10.0 g/dL and *major* surgery
- Hemoglobin of <8.0 g/dL and *symptomatic* anemia

<sup>†</sup> Hematocrit estimated by Hb g/dL × 3.

### Guidelines for Pediatric Fresh Frozen Plasma Transfusions

#### INFANTS, CHILDREN, AND ADOLESCENTS

- Severe* clotting factor deficiency and bleeding
- Severe* clotting factor deficiency and an invasive procedure
- Emergency reversal* of warfarin effects
- Dilutional coagulopathy and bleeding
- Anticoagulant protein (antithrombin III, proteins C and S) replacement
- Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura

## Primary Polycythemia (Polycythemia Rubra Vera)

Polycythemia : an RBC mass >25% above the mean normal value (based on body surface area), or hematocrit >60 (in males) or >56 (in females) indicates absolute erythrocytosis.

### Diagnosis of Polycythemia Vera (Primary)

#### MAJOR CRITERIA

1. Increased red cell mass (see text)
2. Arterial O<sub>2</sub> saturation of  $\geq 92\%$
3. Palpable splenomegaly

#### MINOR CRITERIA

1. Platelet count of  $>400 \times 10^9/L$
2. Leukocytosis of  $>12 \times 10^9/L$
3. Increased leukocyte alkaline phosphatase
4. Increased vitamin B<sub>12</sub> ( $>900 \text{ pg/mL}$ ) or unbound B<sub>12</sub> binding capacity ( $>2,200 \text{ pg/mL}$ )

#### DIAGNOSIS

All 3 major criteria

1, 2, and 2 minor criteria

#### CLINICAL MANIFESTATIONS.

- Hepatosplenomegaly.
- Erythrocytosis may cause hypertension, headache, shortness of breath, or neurologic symptoms.
- Granulocytosis may cause diarrhea or pruritus from histamine release.
- Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage.

#### TREATMENT.

- Phlebotomy is the initial treatment of choice.
- Iron supplementation to prevent viscosity problems from microcytosis.
- Antiplatelet agents (aspirin) may reduce the risks of thrombosis.
- Antiproliferative treatments (hydroxyurea, anagrelide, interferon- $\alpha$ ) may be helpful.

### Secondary Polycythemia

Secondary polycythemia is diagnosed when true polycythemia is caused by another physiologic process.





## LYMPHOPENIA

The normal lymphocyte count in children <2 yr of age is 3,000–9,500/ $\mu$ L and in adults is 1,000–4,800/ $\mu$ L. At 6 yr of age, the lower limit of normal is 1,500/ $\mu$ L.

The average number of CD4 T lymphocytes in adult blood is 1,100/ $\mu$ L (range, 300–1,300/ $\mu$ L), and the average number of CD8 (suppressor) T lymphocytes is 600/ $\mu$ L (range, 100–900/ $\mu$ L), with the normal CD4:CD8 ratio of 1.8–2.0.

## CAUSES OF LYMPHOCYTOPENIA.

### ACQUIRED CAUSES

#### Infectious Diseases

AIDS

Viral hepatitis

Influenza

Tuberculosis

Typhoid fever

Sepsis

#### Iatrogenic

Immunosuppressive therapy

Corticosteroids

#### Systemic and Other Diseases

Systemic lupus erythematosus

Renal failure

Sarcoidosis

Aplastic anemia

#### Dietary Deficiency

### INHERITED CAUSES

Aplasia of lymphopoietic stem cells

SCID associated with defect in IL-2 receptor  $\gamma$ -chain OR deficiency of ADA

Ataxia-telangiectasia

Wiskott-Aldrich syndrome

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## OSTEOPETROSIS

### *Pathogenesis:*

Two main forms of osteopetrosis have been delineated:

- A severe, autosomal recessive form : mutations in a gene (TCIRG1)
- A mild, autosomal dominant form : Mutations of the gene CLCN7

Both types of mutations lead to disturbances of acidification needed for normal osteoclast function.

### CLINICAL MANIFESTATIONS.

- ✦ narrowing of cranial nerve foramina and encroachment on marrow spaces, which results in secondary complications, such as optic and facial nerve dysfunction, and
- ✦ Anemia accompanied by compensatory extramedullary hematopoiesis in the liver and spleen with HSM.
- ✦ Dental problems, osteomyelitis of the mandible, and pathologic fractures
- ✦ Macrocephaly, hepatosplenomegaly, deafness and blindness.
- ✦ May have normal intelligence despite hearing and visual loss.

### *Investigations.*

Skeletal radiographs reveal :

1. a generalized increase in bone density and clubbing of metaphyses (diffuse bone sclerosis and bone within a bone appearance).
2. Alternating bands of lucent and dense bands produce a sandwich appearance to vertebral bodies.

### TREATMENT.

- Bone marrow transplantation.
- Calcitriol and interferon- $\gamma$  have also been used with some benefit.
- Dental care.
- Transfusions for anemia.
- Antibiotic treatment of infections.

*Good luck*

# Nephrology

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## POST STREPTOCOCCAL GLOMERULONEPHRITIS (التهبة الكلوية)

### DIAGNOSIS.

- ❖ Urinalysis: RBC casts, proteinuria, and polymorphonuclear leukocytes.
- ❖ A mild normochromic anemia may be present from hemodilution and low-grade hemolysis.
- ❖ The serum C3 level is usually reduced in the acute phase and returns to normal 6–8 wk after onset.
- ❖ Confirmation of the diagnosis requires clear evidence of invasive streptococcal infection (A positive throat culture report or detects antibodies to streptolysin O, DNase B, hyaluronidase and streptokinase).

### TREATMENT.

- Management of ARF & HTN: (Sodium restriction, diuresis , calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors).
- Although a 10-day course of systemic antibiotic therapy with penicillin is recommended.

### PROGNOSIS.

- Complete recovery occurs in more than 95% of children with acute poststreptococcal glomerulonephritis.
- Mortality: acute renal failure, cardiac failure, and hypertension.

### Causes of hypocomplementemic nephritis:

- 1) Acute post-infectious GN (usually APSGN).
- 2) GN associated shunt nephritis
- 3) GN associated bacterial endocarditis.
- 4) Membranoproliferative GN
- 5) Lupus GN.
- 6) Some genetic causes of HUS.

# Thrombotic Thrombocytopenic Purpura

## Etiology

The majority of cases of TTP are caused by an acquired deficiency of a metalloproteinase (ADAMTS-13) that is responsible for cleaving the high molecular weight multimers of VWF and appears to play a pivotal role in the evolution of the thrombotic microangiopathy.

## Clinical manifestations:

Thrombotic thrombocytopenic purpura (TTP) is a rare pentad of:

1. Fever.
2. Microangiopathic hemolytic anemia.
3. Thrombocytopenia.
4. Abnormal renal function.
5. Central nervous system changes (aphasia, blindness, seizures, weakness, pain, emesis).

## Laboratory findings

- ✦ Microangiopathic hemolytic anemia: schistocytes, spherocytes, helmet cells, and an elevated reticulocyte count in association with thrombocytopenia.
- ✦ Coagulation studies are usually nondiagnostic.
- ✦ Blood urea nitrogen and creatinine are usually elevated.

## Treatment

- Plasmapheresis (plasma exchange), which is effective in 80–95% of cases.
- Corticosteroids and splenectomy are reserved for refractory cases.

## POST STREPTOCOCCAL GLOMERULONEPHRITIS (التهاب الكلى)

### DIAGNOSIS.

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## Sterile Pyuria

Definition: Sterile pyuria is the presence of elevated numbers of white cells ( $>10$  white cells/mm<sup>3</sup>) in urine which appears sterile using standard culture techniques.

### Causes of sterile pyuria

1. A recently (within last 2 weeks) treated urinary tract infection (UTI) or inadequately treated UTI.
2. UTI with 'fastidious' organism, e.g. *Neisseria gonorrhoeae*.
3. Renal tract tuberculosis or chlamydial urethritis.
4. False negative culture due to contamination with antiseptic.
5. Contamination of the sample with vaginal leukocytes.
6. Interstitial nephritis: sarcoidosis (lymphocytes not neutrophils).
7. Urinary tract stones.
8. Renal papillary necrosis: diabetes, sickle cell disease, analgesic nephropathy.
9. Urinary tract neoplasm, including renal cancer and bladder cancer.
10. Polycystic kidneys.
11. Interstitial cystitis.
12. Prostatitis.
13. Other reported associations include appendicitis, systemic lupus erythematosus and Kawasaki disease.
14. Fever and dehydration.

### Investigations

- Urinalysis: Urine Dipstick Analysis. Positive nitrite test +/- positive leukocyte esterase test. Haematuria and proteinuria occur in urinary tract infection (UTI).
- Urine culture and sensitivities.
- History of sexually transmitted disease: chlamydia and *N. gonorrhoeae*.
- Polymerase chain reaction (PCR) testing: *Chlamydia trachomatis*, mycoplasma and ureaplasma infections.
- Always consider tuberculosis; culture for AFBs (3 early morning urine samples).
- Cystoscopy may be required to exclude non-infective causes.

### Management

Management of any identified underlying cause.

*Good luck*

# Neurology

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## Differential Diagnosis of Acute Flaccid Paralysis هام جدا جدا

### ANTERIOR HORN CELLS OF SPINAL CORD

Poliomyelitis (wild and VAPP)

Nonpolio enterovirus

West Nile virus

### OTHER NEUROTROPIC VIRUSES

Rabies virus

Varicella-zoster virus

Japanese encephalitis virus

### GUILLAIN-BARRÉ syndrome

Traumatic causes and other CNS diseases

Acute inflammatory polyradiculoneuropathy

Acute motor axonal neuropathy

Intramuscular gluteal injection

Acute transverse myelitis

Epidural abscess

Spinal cord compression; trauma

### NEUROPATHIES

Exotoxin of *Corynebacterium diphtheriae*

Toxin of *Clostridium botulinum*

Tick bite paralysis

Neuromuscular junction diseases

Myasthenia gravis

### DISORDERS OF MUSCLE

Polymyositis

Viral myositis

### METABOLIC DISORDERS

Hypokalemic periodic paralysis

### ICU WEAKNESS

Critical illness polyneuropathy

# Causes of Stroke in Children

## I. Cardiac Disease

### A. Congenital

1. Aortic stenosis
2. Mitral stenosis; mitral prolapse
3. Ventricular septal defects
4. Patent ductus arteriosus
5. Cyanotic congenital heart disease involving right-to-left shunt

### B. Acquired

1. Endocarditis (bacterial, systemic lupus erythematosus)
2. Kawasaki disease
3. Cardiomyopathy
4. Atrial myxoma
5. Arrhythmia
6. Paradoxical emboli through patent foramen ovale
7. Rheumatic fever
8. Prosthetic heart valve

## II. Hematologic Abnormalities

### A. Hemoglobinopathies

1. Sickle cell (SS) disease
2. Sickle (SC) disease

### B. Polycythemia

### C. Leukemia/lymphoma

### D. Thrombocytopenia

### E. Thrombocytosis

### F. Disorders of coagulation

1. Protein C deficiency
2. Protein S deficiency
3. Factor V Leiden
4. Antithrombin III deficiency
5. Lupus anticoagulant

#### IV. Metabolic Disease Associated with Stroke

- A. Homocystinuria
- B. Pseudoxanthoma elasticum
- C. Fabry disease
- D. Sulfite oxidase deficiency
- E. Mitochondrial disorders
  - 1. MELAS
  - 2. Leigh syndrome
- F. Ornithine transcarbamylase deficiency

#### V. Intracerebral Vascular Processes

- A. Ruptured aneurysm
- B. Arteriovenous malformation
- C. Fibromuscular dysplasia
- D. Moyamoya disease
- E. Migraine headache
- F. Postsubarachnoid hemorrhage vasospasm
- G. Hereditary hemorrhagic telangiectasia
- H. Sturge-Weber syndrome
- I. Carotid artery dissection
- J. Post varicella

#### VI. Trauma and Other External Causes

- A. Child abuse
- B. Head trauma/neck trauma
- C. Oral trauma
- D. Placental embolism
- E. ECMO therapy

## KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY).

### Definition :

-Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. KD is a disorder of myelin destruction rather than abnormal myelin formation.

cause: The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside  $\beta$ -galactosidase.

### Clinical picture:

The symptoms of KD become evident in the 1st few months of life (most die in first 2 yrs) and include:

- ☒ Excessive irritability and crying.
- ☒ Unexplained episodes of hyperpyrexia.
- ☒ Feeding problems, vomiting, and failure to thrive.
- ☒ Alterations in body tone with rigidity and opisthotonos.
- ☒ Visual inattentiveness and blindness due to optic atrophy.
- ☒ In the later stages of the illness, blindness, deafness, absent deep tendon reflexes, and decerebrate rigidity.
- ☒ *Late-onset KD* : Patients present with optic atrophy and cortical blindness. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent.

### Investigations :

- CT scan, MRI and magnetic resonance spectroscopy.
- Cerebrospinal fluid (CSF) shows an elevated protein content.
- The nerve conduction velocities are markedly delayed due to segmental demyelination of the peripheral nerves.
- The VEPs decrease gradually in amplitude.
- The ABRs are characterized by the presence of only waves I and II.
- Prenatal diagnosis : assay of galactocerebroside  $\beta$ -galactosidase activity in chorionic villi or in cultured amniotic fluid cells.

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# METACHROMATIC LEUKODYSTROPHY

## DEFINITION AND PATHOGENESIS:

- ☒ This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity
- ☒ The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate causing myelin breakdown and destruction of oligodendroglia.

## CLINICAL MANIFESTATION

### Late infantile

- ☒ Insidious onset of gait disturbances between 1 and 2 yr of age.
- ☒ The extremities are hypotonic, and the deep tendon reflexes are absent or diminished
- ☒ Deterioration in intellectual function becomes apparent.
- ☒ The speech is slurred and dysarthric, and the child appears dull and apathetic.
- ☒ Visual fixation is diminished, nystagmus is present, and optic atrophy.
- ☒ Feeding and swallowing are impaired due to pseudobulbar palsies.

### Diagnosis :

1. Progressive changes in the VEPs, ABRs, and somatosensory-evoked potentials (SSEPs), and the nerve conduction velocities (NCVs) of the peripheral nerves are significantly reduced.
2. CT and MRI images of the brain: diffuse symmetric attenuation of the cerebellar and cerebral white matter.
3. Examination of the CSF shows an elevated protein content.

### Juvenile MLD

It has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5–10 yr of age.

Adult MLD :It occurs from the 2nd to 6th decade. Abnormalities in memory, psychiatric disturbances, and personality changes are prominent features. Slowly progressive neurologic signs, including spasticity, dystonia, optic atrophy, and generalized convulsions.

## Adrenoleukodystrophy

**Definition:** The adrenoleukodystrophies consist of a group of CNS degenerative disorders that are often associated with adrenal cortical insufficiency and are inherited by X-linked recessive transmission.

### Types:

*I- Classic adrenoleukodystrophy (ALD)* becomes symptomatic between 5 and 15 yr of age and caused by accumulation of very long chain fatty acids in neural tissue and adrenals due to mutations in the *ABCD1* gene.

### Clinical picture :

- ✗ Generalized seizures are common in the early stages.
- ✗ Upper motor neuron signs include spastic quadriparesis and contractures.
- ✗ Ataxia.
- ✗ Marked swallowing disturbances secondary to pseudobulbar palsy.
- ✗ Hypoadrenalism is present in  $\approx 50\%$  of cases, and adrenal insufficiency characterized by abnormal skin pigmentation.

### DIAGNOSIS:

- ✦ When ALD is suspected based on clinical symptoms, the initial testing usually includes plasma very long chain fatty acid (VLCFA) determination using gas chromatography-mass spectrometry.
- ✦ CT scans and MRI studies of patients indicate periventricular demyelination beginning posteriorly; this advances progressively to the anterior regions of the cerebral white matter.
- ✦ ABRs, VEPs, and SSEPs may be normal initially but ultimately show prolonged latencies and abnormal waveforms.

### TREATMENT & PROGNOSIS

- Death supervenes within 10 yr of the onset of the neurologic signs.
- Bone marrow transplant can prevent the progression of the disease when done at an early stage before clinical signs develop.
- In addition, administration of Lorenzo's oil, to neurologically abnormal boys <6 yr of age with a normal MRI of the brain may reduce the probability of developing neurological abnormalities later in life.



## Acute Disseminated Encephalomyelitis (ADEM)

### DEFINITION:

ADEM is a monophasic, immune-mediated demyelinating disorder that can follow immunizations or more often infections including rubeola, rubella, varicella, herpes zoster, mumps, *Mycoplasma pneumoniae*, or, more commonly. Latent period=20days.

- ADEM are more common in females 85%.

### CLINICAL PICTURE:

- Focal neurologic signs.
- Motor weakness.
- Acute seizures.
- Encephalopathy OR coma.
- Brain edema.
- Fever, lethargy, vomiting, ataxia and nystagmus.
- Myelopathy.

### Investigations :

1. MRI typically shows T2 enhancing disseminated multifocal lesions in the white matter, basal ganglia, thalamus, and brainstem consistent with demyelination.
2. Examination of CSF often shows a monocytic and lymphocytic pleocytosis.
3. Thrombocytosis.

### Treatment

- a) High-dose intravenous corticosteroids (IV methylprednisolone, 30 mg/kg/day for >30 kg of body weight, and 1 g/day for >30 kg of body weight for 3–5 days, followed by oral prednisolone [1 mg/kg/day] over 10 days) may result in improvement.
- b) Positive responses to intravenous immunoglobulin (IVIG) have also been reported.

### Prognosis

Outcome after an episode of ADEM is generally good with >70% of children recovering without disability within 6 mo.

# Multiple Sclerosis (MS)

## Definition:

MS is a chronic and generally remitting-relapsing disorder characterized by multiple white lesions in the CNS separated by time and location in the brain.

**Cause:** unknown, but interactive genetic, immunologic, and infectious factors are probably responsible. A family history in ~20%.

## Clinical picture:

The most frequent presenting signs are:

- Unilateral weakness with upper motor neuron signs.
- Sensory abnormalities.
- Ataxia.
- Paresthesias.
- Visual symptoms including diplopia, nystagmus, or sudden visual loss due to optic neuritis are also important early manifestations of MS.
- Headache, fatigue, dysarthria, or myelopathy with a sensory level and neurogenic bladder can also be present.
- Neuromyelitis optica (Devic disease) is a variant of classic MS and consists of *optic neuritis* and *transverse myelitis*, which occur conjointly.
- Although a 1st attack of MS may be suspected after an initial episode, the diagnosis is not made until a 2nd clinical episode occurs after a period of a month or a new white lesion appears on magnetic resonance imaging (MRI) after 3 mo.

## Investigations:

1. The pathology of MS consists of demyelination with the formation of plaques. A high percentage of pediatric patients have T2 enhancing lesions in the corpus callosum and periventricular white matter.
2. The cerebrospinal fluid (CSF) often contains oligoclonal bands.

## Treatment:

- a) High-dose intravenous methylprednisolone.
- b) Aggressive therapy of optic neuritis with prednisone.
- c) Rehabilitative care is useful.
- d) Disease-modifying interferon therapies can decrease disease activity (Interferon- $\beta$ , glatiramer acetate, and natalizumab).

## Brain Abscess

Predisposing factors: most common in children between 4 and 8 yr and neonates.

- Congenital heart disease with right-to-left shunts (especially tetralogy of Fallot)
- Meningitis.
- Chronic otitis media and mastoiditis, sinusitis, soft tissue infection of the face or scalp, orbital cellulitis, dental infections.
- Penetrating head injuries.
- Immunodeficiency states.
- Infection of ventriculoperitoneal shunts.

### ETIOLOGY.

- a) Streptococci, anaerobic organisms (gram-positive cocci, *Bacteroides* spp.), and gram-negative aerobic bacilli (*Haemophilus aphrophilus*, *H. parainfluenzae*, *H. influenzae*).
- b) *Citrobacter* is most common in neonates.
- c) Fungal abscesses (*Aspergillus*, *Candida*) are more common in immunosuppressed patients.

### CLINICAL MANIFESTATIONS.

- o The early stages: low-grade fever, headache, and lethargy.
- o Advanced stages: vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), ataxia, nystagmus and coma may develop.

### DIAGNOSIS.

- ⊗ CBC: The peripheral white blood cell count can be normal or elevated, and the blood culture is positive in ≈10% of cases.
- ⊗ Examination of the cerebrospinal fluid (CSF) shows variable results; the white blood cells and protein may be minimally elevated or normal, and the glucose level may be low.
- ⊗ The electroencephalogram (EEG) shows corresponding focal slowing.
- ⊗ CT with contrast and MRI are the most reliable methods of demonstrating cerebritis and abscess formation. MRI is the diagnostic test of choice.

### TREATMENT.

1. Medical (The duration of antibiotic therapy depends on the organism and response to treatment, but is usually 4–6 wk).
  - A. When the cause is unknown, the combination of vancomycin, a 3rd-generation cephalosporin, and metronidazole is commonly used.
  - B. When cyanotic congenital heart disease is the predisposing factor, ampicillin-sulbactam alone or a 3rd-generation cephalosporin plus metronidazole may be used.
  - C. Abscesses secondary to an infected ventriculoperitoneal shunt may be initially treated with vancomycin and ceftazidime.

Good luck

# Pulmonology

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## Differential Diagnosis of Wheezing in Infancy

### INFECTION

#### Viral

Respiratory syncytial virus (RSV)

Human metapneumovirus

Parainfluenza

Adenovirus

Influenza

Rhinovirus

#### Other

Chlamydia trachomatis

Tuberculosis

### ASTHMA

### ANATOMIC ABNORMALITIES

#### Central airway abnormalities

Malacia of the larynx, trachea, and/or bronchi

Tracheoesophageal fistula (specifically H-type fistula)

Laryngeal cleft (resulting in aspiration)

Extrinsic airway anomalies resulting in airway compression

Vascular ring or sling

Mediastinal lymphadenopathy from infection or tumor

Mediastinal mass/tumor

Esophageal foreign body

#### Intrinsic airway anomalies

Airway hemangioma, other tumor

Cystic adenomatoid malformation

Bronchial/lung cyst

Congenital lobar emphysema

Aberrant tracheal bronchus

Sequestration

Congenital heart disease with left-to-right shunt (increased pulmonary edema)

Foreign body

## Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN SYMPTOM	NONRESPIRATORY CAUSES	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease	Right-to-left shunt	Neonatal onset, lack of response to oxygen
	Methemoglobinemia	Increased levels of metHgb interfere with delivery of oxygen to tissues	Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal SpO <sub>2</sub>
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety or depression
Exercise intolerance	Anemia	Inadequate oxygen deliver to tissues	Pallor, tachycardia, history of bleeding, history of inadequate diet
	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding causes appearance of pulmonary origin	History and physical examination suggest nasal source, normal chest examination, and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source, normal chest examination and chest radiography

## Atypical pneumonia

(Walking pneumonia)

### Cause

The most common causative organisms are (often intracellular living) bacteria:

#### I. Bacterial

- a) Chlamydophila pneumoniae.
- b) Chlamydia psittaci
  - a. Causes psittacosis.
- c) Coxiella burnetii
  - a. Causes Q fever.
- d) Francisella tularensis
  - a. Causes tularemia.
- e) Legionella pneumophila
  - a. Causes legionellosis or Legionnaires' disease.
- f) Mycoplasma pneumoniae

#### II. Viral

- a) Respiratory Syncytial Virus (RSV),
- b) Influenza A and B,
- c) Parainfluenza,
- d) Adenovirus.
- e) Severe acute respiratory syndrome (SARS)
- f) Measles

#### III. Fungal: pneumocystis carinii

## Mycoplasma Pneumoniae

Age:- school-aged children & young adult

TRANSMISSION:- Infection occurs through the respiratory route by large droplet spread.  
The incubation period is 1-3 wk.

### Etiology:

M.pneumonia are smallest self replication.

### Pathology:

Bronchopneumonia or interstitial.

### CLINICAL MANIFESTATIONS:-

- Gradual onset of FAHM, rhinorrhea and sore throat.
- Cough usually worsen during 1<sup>st</sup> 2wks.
- Cough initially non productive then frothy white sputum.
- Symptom: severity > physical sign.
- Auscultation: fine crepitation.
- Symptom gradually resolve within 3-4 wks

### DIAGNOSIS:- Non specific

#### Chest X-ray:

- ✓ Bronchopeumonia, interstitial involvement, most common lower lobe with unilateral central dense infiltration in 75%.
- ✓ Hilar lymphadenopathy 33%

CBC, CRP, ESR: normal CBC, elevated ESR

#### Other:

#### Serology:

- ✓ IGM M.pneumonia AB achieved in 2<sup>nd</sup> wks.
- ✓ Demonstrated of M.pneumonia in sputum by PCR.
- ✓ Positive coomb's test with significant titer of cold hemagglutinin (1:64 or more in 50% of patient)
- ✓ Hemolysis or reticulocytosis occurring 2-3 wks after onset.
- ✓ Thrombocytopenia & cogulation defect rare.

### TREATMENT:

- ✓ M.pneumonia usually mild & hospital infrequent.
- ✓ M.pneumonia sensitivity to erythromycin, clarithromycin, azithromycin.
- ✓ Organism resistant to penicillin due to absence of cell wall.

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## Risk factors for Recurrent Pneumonia

### Hereditary Disorders

- Cystic fibrosis
- Sickle cell disease

### Disorders of Immunity

- AIDS
- Bruton agammaglobulinemia
- Selective IgG subclass deficiencies
- Common variable immunodeficiency syndrome
- Severe combined immunodeficiency syndrome

### Disorders of Leukocytes

- Chronic granulomatous disease
- Hyperimmunoglobulin E syndrome (Job syndrome)
- Leukocyte adhesion defect

### Disorders of Cilia

- Immotile cilia syndrome
- Kartagener syndrome

### Anatomic Disorders

- Sequestration
- Lobar emphysema
- Esophageal reflux
- Foreign body
- Tracheoesophageal fistula (H type)
- Gastroesophageal reflux
- Bronchiectasis
- Aspiration (oropharyngeal incoordination)

## Neuromuscular Diseases with Respiratory Dysfunction

### *Etiology*

- High level spinal cord injury
- Poliomyelitis
- Guillain-Barré syndrome
- Duchenne muscular dystrophy
- Spinal muscular atrophy
- Congenital myotonic dystrophy
- Myasthenia gravis
- Charcot-Marie-Tooth disease

### *Pathogenesis*

- » In the absence of competent mucociliary clearance, mucous plugs will compromise pulmonary function and lead to chronic infection and fibrosis
- » Respiratory muscle weakness : hypoxemia, pulmonary hypertension, and, eventually, cor pulmonale.

### *CLINICAL MANIFESTATIONS*

- Acute respiratory distress with dyspnea, agitation, diaphoresis, and cyanosis.
- Lung exam.: decrease air entry, wheezes and crepitations.
- The restrictive lung disease : kyphoscoliosis.

### *Diagnosis :*

- The presence of hypoxemia is documented by ABG and monitored by pulse oximetry.
- CXR/CT chest: may reveal the presence of segmental or lobar atelectasis.
- PFT: decreases in total lung capacity, vital capacity and an increase in residual volume.
- Polysomnography.
- Exercise testing (in selected cases).

## $\alpha_1$ -Antitrypsin Deficiency

### PATHOGENESIS:-

-It is an autosomal recessive disease. Normal individuals have Pi type MM. while early adult onset emphysema is associated with PiZZ type.

- $\alpha_1$ -Antitrypsin and other serum antiproteases are important in the inactivation of proteolytic enzymes released from dead bacteria or leukocytes in the lung. Deficiency of antiproteases leads to subsequent development of emphysema.

### CLINICAL MANIFESTATIONS:-

- Most patients who have the PiZZ defect have little or no detectable pulmonary disease during childhood.
- A few have early onset of chronic pulmonary symptoms, including dyspnea, wheezing, and cough, and panacinar emphysema by lung biopsy.
- Smoking greatly increases the risk of emphysema developing in mutant Pi types.
- Physical examination in childhood is usually normal. It very rarely reveals growth failure, and clubbing.

### Chest exam.

- ✓ Inspection: increased anteroposterior diameter of the chest
- ✓ Percussion: hyperresonant percussion note, crackles in active infection.
- ✓ Palpation: Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.
- ✓ Auscultation: crackles in active infection

### LABORATORY FINDINGS:-

- ✦ Chest X-ray: overinflation with depressed diaphragm.
- ✦ Chest CT may show more hyperexpansion in the lower lung zones, with occasional bronchiectasis.
- ✦ Serum immunoassay measures low levels of  $\alpha_1$ -antitrypsin normal  
serum levels are 180–280 mg/dL.
- ✦ Serum electrophoresis reveals the phenotype, and genotype is determined by PCR.

### TREATMENT:-

- ☒ Enzyme replacement:-
  - ✓ Purified blood-derived human enzyme: 60 mg/kg IV weekly
  - ✓ Pure  $\alpha_1$ -Antitrypsin produced by recombinant DNA technology: aerosolize form
- ☒ Standard supportive therapy for chronic lung disease:
  - ✦ Aggressive treatment of pulmonary infection,
  - ✦ Routine use of pneumococcal and influenza vaccines,
  - ✦ Bronchodilators,
  - ✦ Advice about the serious risks of smoking.

## Primary Ciliary Dyskinesia (Immotile Cilia Syndrome)

### Definition

- Primary ciliary dyskinesia (PCD) malfunction of airway cilia results from inherited structural abnormalities of that lead to repeated and chronic lung and sinus infections.
- Kartagener syndrome: situs inversus, chronic sinusitis and otitis, and airway disease leading to bronchiectasis.

### PATHOLOGY:-

- Lack of dynein arms.
- Microtubular transposition.
- Abnormal length of cilia.
- Absence of cilia with brush border metaplasia.

### CLINICAL MANIFESTATIONS:-

*Newborn* : respiratory distress may occur during newborn period.

*Older children*:

- ✓ Productive cough.
- ✓ Repeat attack of acute otitis media and acute sinusitis. conductive hearing loss is common.
- ✓ Nasal polyp or clubbing in about 20% of patient.
- ✓ Disease can progress to diminished exercise tolerance, weight loss, bronchiectasis.
- ✓ Male are frequent infertile, absent or poor sperm motility.

### DIAGNOSIS:-

- ❖ Chest radiographs or CT imaging : Atelectasis , consolidation OR bronchiectasis.
- ❖ Pulmonary function testing of older children: typical obstructive pattern.
- ❖ Plain X-ray or CT imaging on sinuses: show involvement of paranasal sinuses.
- ❖ Mucociliary clearance assessment: in cooperative children recording the time to taste perception of a saccharin particle placed on the inferior nasal turbinate (normal is <30 min).
- ❖ Ultrastructural evaluation on electronmicroscopy the gold standard.
- ❖ Exhaled nitric oxide (NO): is markedly decreased in patients with PCD (high level suggest cystic fibrosis).

## Pulmonary Hemosiderosis

**Definition:** a triad of iron-deficiency anemia, hemoptysis, and the alveolar infiltrates on chest radiographs.

### ETIOLOGY.

Primary pulmonary hemosiderosis (PPH): IPH(idiopathic), Goodpasture syndrome , and Heiner syndrome (cow's milk hyperreactivity).

Secondary pulmonary hemosiderosis such as

- ✦ Congestive heart failure.
- ✦ Pulmonary hypertension.
- ✦ Mitral valve stenosis.
- ✦ Collagen vascular: Systemic lupus erythematosus. rheumatoid arthritis. Wegener granulomatosis, and Henoch-Schönlein purpura.
- ✦ Celiac disease.
- ✦ Postinfectious processes such as hemolytic-uremic syndrome and immunodeficiency..
- ✦ Environmental exposures, chemicals, and food allergens

### LABORATORY FINDINGS AND DIAGNOSIS.

- CBC: a microcytic, hypochromic anemia and WBCs may be elevated.
- The reticulocyte count is elevated.
- Serum iron is reduced. Iron-binding capacity is generally elevated.
- A stool specimen can be heme-positive secondary to swallowed blood.
- Renal and liver function should be reviewed.
- A urinalysis: nephritis.
- A coagulation profile.
- Quantitative immunoglobulins (including IgE), and complement studies are recommended.
- Testing for ANCA, antinuclear antibody (ANA), anti-double stranded DNA, rheumatoid factor, antiphospholipid antibody, and (antiGBM).
- Increase (ESR).
- Sputum or pulmonary secretions should be analyzed for significant evidence of blood or hemosiderin-laden macrophages (HLM).
- Lung biopsy.
- CXR & CT chest.
- Pulmonary function testing.

### TREATMENT.

- ☒ Supportive therapy including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products may be warranted
- ☒ In IPH(idiopathic pulmonary hmg): systemic corticosteroids or immunosuppressive agents such as cyclophosphamide or azathioprine.
- ☒ Lung transplant for end stage.

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## Eosinophilic Lung Disease (Löffler Syndrome)

### Definition:

Eosinophilic lung diseases : pulmonary infiltrates and circulating or tissue eosinophilia.

### Types:

- Simple pulmonary eosinophilia (Löffler syndrome): most common cause.
- Prolonged pulmonary eosinophilia.
- Tropical pulmonary eosinophilia.
- Pulmonary eosinophilia with asthma.
- Polyarteritis nodosa.
- Chronic eosinophilic pneumonia.
- Acute eosinophilic pneumonia.
- Churg-Strauss syndrome.
- Allergic bronchopulmonary aspergillosis.
- Idiopathic hypereosinophilia syndrome.

### Etiology :

Parasite infections (*Ascaris lumbricoides*) and drug reactions

Drugs: Sulfasalazine, penicillin, ampicillin, ibuprofen, and cromolyn

### CLINICAL MANIFESTATIONS.

- ✦ Malaise
- ✦ Chronic cough
- ✦ Intermittent fevers
- ✦ Dyspnea
- ✦ Wheezing
- ✦ Abdominal pain
- ✦ Rash
- ✦ Weight loss.

### DIAGNOSIS.

**TRIAD:** clinical manifestations , associated blood eosinophilia and chest radiographic findings.

- ✓ CXR: nonspecific interstitial, alveolar, or mixed infiltrates.
- ✓ Presence of pulmonary infiltrates and eosinophilia on bronchoalveolar lavage.
- ✓ Presence of parasitic larvae in bronchoscopic or gastric lavage.
- ✓ Lung biopsy.

### TREATMENT.

- Parasite and drug-induced PIE syndromes have a good prognosis and resolve spontaneously with supportive care and removal of exposure OR anti helminthic drugs.
- Acute eosinophilic pneumonia and chronic eosinophilic pneumonia :a course of corticosteroids.

# Pulmonary Alveolar Proteinosis

## Definition:

It is a disorder characterized by the intra-alveolar accumulation of pulmonary surfactant lipoproteins.

## Histopathology

On histopathologic examination, distal air spaces are filled with a granular, eosinophilic material that stains positively with periodic acid-Schiff reagent and is diastase resistant.

## Types:

- a) A fulminant, often fatal form presenting shortly after birth (termed congenital PAP)
- b) A gradually progressive type presenting in older infants and children (primary or idiopathic (acquired)).

## ETIOLOGY:

The early onset of the neonatal form of PAP: due to mutations of

- 1) Surfactant protein B (SP-B).
- 2) Surfactant protein C (SP-C).
- 3)  $\beta$  chain of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor.
- 4) Adenosine triphosphate (ATP)-binding cassette transporter (ABCA3) genes.
- 5) It may occur in patients with lysinuric protein intolerance (LPI).

## Pathophysiology:

Primary (idiopathic) PAP in adults is an autoimmune disease mediated by autoantibodies against GM-CSF. GM-CSF is essential in regulating macrophage function and clearance of surfactant.

Secondary alveolar proteinosis: due to infection, particularly in immunocompromised individuals or Environmental exposures to dust, silica, and chemicals.

## CLINICAL MANIFESTATIONS.

- o Congenital form of PAP: lead to respiratory failure, including pneumonia, generalized bacterial infection, respiratory distress syndrome, and total anomalous pulmonary venous return with obstruction.
- o Idiopathic (acquired) alveolar proteinosis: dyspnea, fatigue, cough, weight loss, chest pain, or hemoptysis. In the later stages, cyanosis and digital clubbing may be seen.

# Interstitial Lung Diseases

## Definition

It includes a group of uncommon, heterogeneous, familial, or sporadic diseases that cause disruption of alveolar gas exchange and symptoms of restrictive lung disease.

## Pathophysiology

In ILD, the initial injury causes damage to the alveolar epithelium and capillary endothelium. Abnormal healing of injured tissue may be more prominent than inflammation in the initial steps of the development of chronic ILD.

## CLASSIFICATION

### Pediatric Interstitial Lung Diseases

#### INTERSTITIAL LUNG DISEASES OF KNOWN ETIOLOGY

Aspiration syndromes

Chronic infection (viral, bacterial, fungal, parasitic)

- Immunocompetent host
- Immunocompromised host

Bronchopulmonary dysplasia

Hypersensitivity pneumonitis (drugs, environment or occupation associated)

Lymphangioleiomyomatosis

Surfactant protein B or C deficiency

#### INTERSTITIAL LUNG DISEASES OF UNKNOWN ETIOLOGY

Usual interstitial pneumonitis (UIP)

Desquamative pneumonitis (DIP)

Lymphocytic interstitial pneumonitis (LIP) and related disorders

Nonspecific interstitial pneumonitis

Pulmonary hemosiderosis

Goodpasture disease

Pulmonary infiltrates with eosinophilia

Pulmonary interstitial glycogenosis (PIG)

Neuroendocrine cell hyperplasia of infancy (NEHI)

Bronchiolitis obliterans

Bronchiolitis obliterans with organizing pneumonia (BOOP)

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## DIAGNOSIS.

- 1) Chest radiographic abnormalities can be classified as interstitial, reticular, nodular, reticulonodular, or honeycombed.
- 2) High-resolution CT (HRCT) of the chest better defines the extent and distribution of disease .
- 3) Pulmonary function tests(restrictive lung disease) : Functional residual capacity (FRC) is reduced but usually less than vital capacity (VC) and total lung capacity (TLC). Diffusion of carbon monoxide (DLCO) is usually normal.
- 4) Bronchoalveolar lavage (BAL): for pulmonary alveolar proteinosis.
- 5) Transthoracic lung biopsy for histopathology is usually the final step and is necessary for a conclusive diagnosis.

## TREATMENT.

- a) Supplemental oxygen for hypoxia.
- b) Adequate nutrition for growth failure.
- c) Antimicrobial treatment may be necessary for intercurrent infections.
- d) Some patients may be responsive to bronchodilators.
- e) Anti-inflammatory treatment with corticosteroids remains the initial treatment of choice. The usual dose of prednisone is 1–2 mg/kg/24 hr for 6–8 wk with tapering dictated by clinical response. Alternative, but not adequately evaluated, therapy includes hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, intravenous immunoglobulin, and pulsed high-dose steroids.
- f) Preventive measures include avoidance of all inhalation irritants such as tobacco smoke and, when appropriate, molds and bird antigens.
- g). Supervised pulmonary rehabilitation programs may be helpful.

## Bronchogenic cysts

### OGY AND PATHOLOGY:

hogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut and lined  
ilia d epithelium.

The are more commonly found on the right and near a midline structure (trachea, esophagus,  
1)

### IC MANIFESTATIONS

mp: matic

er, chest pain, and productive cough

ph: ia

gnc: s:

- ⊕ A chest radiograph reveals the cyst, which may contain an air-fluid level .
- ⊕ CT scan or MRI is obtained in most cases to better demonstrate anatomy and extent of lesion  
before surgical resection.

atment :

gic - excision after appropriate antibiotic management even if a symptomatic.

mplications:

- Pressure symptoms
- Secondary infection

*Good luck*

# Cardiology

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## Differential Diagnosis of Chest Pain in Pediatric Patients

### MUSCULOSKELETAL (COMMON)

- Trauma (accidental, abuse)
- Exercise, overuse injury (strain, bursitis)
- Costochondritis (Tietze syndrome)
- Herpes zoster pericardectomy (cutaneous)
- Pleurodynia
- Slipping rib
- Sickle cell anemia vaso-occlusive crisis
- Osteomyelitis (rare)
- Primary or metastatic tumor (rare)

### PULMONARY (COMMON)

- Pneumonia
- Pleurisy
- Asthma
- Chronic cough
- Pneumothorax
- Infarction (sickle cell anemia)
- Foreign body
- Embolism (rare)
- Pulmonary hypertension (rare)
- Tumor (rare)

### GASTROINTESTINAL (LESS COMMON)

- Esophagitis (gastroesophageal reflux, infectious, pill)
- Esophageal foreign body
- Esophageal spasm
- Cholecystitis
- Subdiaphragmatic abscess
- Perihepatitis (Fitz-Hugh-Curtis syndrome)
- Peptic ulcer disease

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## Innocent murmur

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as functional, normal, insignificant, or innocent especially under non basal circumstances (high cardiac output because of fever, infection, anxiety).

### *Types :*

1. The most common innocent murmur is a medium-pitched, vibratory or "musical," relatively short systolic ejection murmur, which is heard best along the left lower and midsternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 yr of age. The intensity of the murmur often changes with respiration and position and may be attenuated in the sitting or prone position
2. Innocent pulmonic murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. They are higher pitched, blowing, brief early systolic murmurs of grade I-II in intensity and are best detected in the 2nd left parasternal space with the patient in the supine position

*Features suggestive of heart disease include murmurs that are :*

- ✓ Pansystolic.
- ✓ Grade III or higher.
- ✓ Harsh, located at the left upper sternal border
- ✓ Associated with an early or midsystolic click or an abnormal 2nd heart sound.

## CAUSES OF PERICARDITIS

### INFECTIOUS

- Viral (coxsackievirus B, Epstein-Barr virus influenza, adenovirus)
- Bacterial (streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma)
- Immune complex (meningococcus, *Haemophilus influenzae*)
- Tuberculosis
- Fungal (histoplasmosis, actinomycosis)
- Parasitic (toxoplasmosis, echinococcosis)

### CONNECTIVE TISSUE DISEASES

- Rheumatoid arthritis
- Rheumatic fever
- Systemic lupus erythematosus
- Systemic sclerosis
- Sarcoidosis
- Wegener granulomatosis

### METABOLIC-ENDOCRINE

- Uremia
- Hypothyroidism

### HEMATOLOGY-ONCOLOGY

- Bleeding diathesis
- Malignancy (primary, metastatic)
- Radiotherapy-induced

### OTHER

- Trauma (penetrating or blunt injury)
- Iatrogenic (catheter related)
- Postpericardiotomy (cardiac surgery)
- Aortic dissection
- Idiopathic

## Acute Pericarditis

### **PATHOPHYSIOLOGY:**

- Pericardial inflammation results in an accumulation of fluid in the pericardial space.
- Cardiac tamponade occurs when the amount of pericardial fluid reaches a level that compromises cardiac function.

### **History & physical examination**

1. A sharp, stabbing sensation over the precordium and often the left shoulder and back; the pain may be exaggerated by lying supine and relieved by sitting, especially leaning forward.
2. Cough, dyspnea, abdominal pain, vomiting, and fever may also occur.
3. The presence of a friction rub is helpful but is a variable sign in acute pericarditis.
4. When the effusion is larger, muffled heart sounds may be the only auscultatory finding.
5. Narrow pulses, tachycardia and neck vein distention.
6. Increased pulsus paradoxus suggest significant fluid accumulation. Pulsus paradoxus is caused by the normal slight decrease in systolic arterial pressure during inspiration. A pulsus paradoxus  $>20$  mm Hg in a child with pericarditis is an indicator of the presence of cardiac tamponade.

### **DIAGNOSIS:**

- ECG(Low voltage of the QRS complexes results from a damping effect of pericardial fluid,mild elevation of ST segments, generalized T-wave inversion, electrical alternans may be present and is demonstrated by a variable QRS complex amplitude).
- CXR:"waterbottle"configuration
- The echocardiogram

### **TREATMENT:**

- Anti-inflammatory agents(steroids or salicylates)
- Pericardiocentesis if tamponade develops.
- Pericardiectomy

*Good luck*

Rheumatology  
&  
Immunology

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# Macrophage activation syndrome

## Definition

The acute development of a profound anemia associated with thrombocytopenia or leukopenia with a high, spiking fever, lymphadenopathy, and hepatosplenomegaly. It is a rare and occasionally fatal complication of systemic JRA.

## Etiology

- (1) A flare of the underlying disease.
- (2) Toxicity of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- (3) Viral infections.
- (4) Drugs: gold salts, sulfasalazine therapy, methotrexate.
- (5) Autologous bone marrow transplantation.

## Diagnosis

Preliminary Diagnostic Guidelines for Macrophage Activation System (MAS) Complicating Systemic Juvenile Idiopathic Arthritis (S-JIA)

### LABORATORY CRITERIA

1. Decreased platelet count ( $\leq 262 \times 10^9/L$ )
2. Elevated levels of aspartate aminotransferase ( $> 59 U/L$ )
3. Decreased white blood cell count ( $\leq 4.0 \times 10^9/L$ )
4. Hypofibrinogenemia ( $\leq 2.5 g/L$ )

### CLINICAL CRITERIA

1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Hemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly ( $\geq 3$  cm below the costal arch)

### HISTOPATHOLOGICAL CRITERION

Evidence of macrophage hemophagocytosis in the bone marrow aspirate

### DIAGNOSTIC RULE

The diagnosis of MAS requires the presence of any 2 or more laboratory criteria or of any 2 or 3 or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of haemophagocytosis may be required only in doubtful cases.

## 10 Warning signs of immunodeficiency

Evaluation of immune function should be initiated for children with clinical manifestations of a specific immune disorder or with unusual, chronic, or recurrent infections such as:

1. One or more systemic bacterial infections (sepsis, meningitis).
2. Two or more serious respiratory or documented bacterial infections (cellulitis, draining otitis media, pneumonia, lymphadenitis) within 1 yr.
3. Serious infections occurring at unusual sites (liver, brain abscess).
4. Infections with unusual pathogens (*Aspergillus*, *Serratia marcescens*, *Nocardia*, *Burkholderia cepacia*).
5. Infections with common childhood pathogens but of unusual severity.
6. >8 ear infections per yr; >2 serious sinus infections per yr.
7. >2 mo treatment with antibiotics with poor results.
8. Failure to thrive with or without chronic diarrhea.
9. The need for intravenous antibiotics to successfully treat an infection usually treated with oral antibiotics.
10. Certain clinical features suggestive of immunodeficiency syndromes:  
DiGeorge anomaly (Hypocalcemia, heart disease, unusual facies).

# Anaphylaxis

**Definition:** Anaphylaxis occurs when there is a sudden release of potent biologically active mediators from mast cells and basophils leading to :

- Cutaneous (urticaria, angioedema, flushing).
- Respiratory (bronchospasm, laryngeal edema).
- Cardiovascular (hypotension, dysrhythmias, myocardial ischemia).
- Gastrointestinal symptoms (nausea, colicky abdominal pain, vomiting, diarrhea).

## ETIOLOGY.

### Common Causes of Anaphylaxis in Children

**Food:** peanuts, tree nuts, milk, eggs, fish, shellfish

**Drugs:** penicillins, cephalosporins, sulfonamides, nonsteroidal anti-inflammatory agents.

**Latex**

**Allergen immunotherapy**

**Vaccinations:** tetanus, measles, mumps, influenza

**Miscellaneous:** radiocontrast media.

**Idiopathic**

## PATHOGENESIS.

-Most cases of anaphylaxis are the result of activation of mast cells and basophils via cell-bound allergen-specific IgE molecules.

-When reexposed to the sensitizing allergen, mast cells and basophils and possibly other cells such as macrophages release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs.

## CLINICAL MANIFESTATIONS AND DIAGNOSIS.

- ✦ Pruritus around the mouth and face.
- ✦ A sensation of warmth, weakness, and apprehension.
- ✦ Flushing, urticaria and angioedema, oral pruritus, tightness in the throat.
- ✦ Dry staccato cough and hoarseness.
- ✦ Periorbital pruritus and nasal congestion.
- ✦ Sneezing, dyspnea, deep cough, and wheezing; nausea.
- ✦ Abdominal cramping, and vomiting.
- ✦ Cutaneous symptoms may be absent in up to 20% of cases.
- ✦ Sudden collapse

## Food Allergy (Food Hypersensitivity)

### Definition:

Food allergy is a group of disorders in which symptoms result from immunologic responses to specific food antigens .

### Pathogenesis:

- a) IgE-mediated reactions are caused by inflammatory mediators released when food antigen binds to specific IgE antibody on mast cells and basophils.
- b) Non-IgE-mediated reactions are cell mediated and develop over hours to days. For some clinical conditions, there appear to be multiple mechanisms involved.

### CLINICAL MANIFESTATIONS.

Food antigen may provoke respiratory, skin, or gastrointestinal symptoms.

### Types :

#### I. IGE-MEDIATED FOOD HYPERSENSITIVITY.

##### 1. Oral Allergy Syndrome.

Contact with the allergen on the oropharynx causes itching or tingling and angioedema of the lips, tongue, palate, and throat.

##### 2. Gastrointestinal Anaphylaxis.

-Rapid onset of nausea, cramping abdominal pain, vomiting, or diarrhea or a combination of these conditions occurs after ingestion of an allergen.

-The most common proteins implicated are milk, egg, peanut, soy, cereal, and fish.

##### 3. Other Nongastrointestinal Manifestations.

Cutaneous—urticaria, angioedema, and atopic dermatitis (eczema);

Respiratory—asthma and rhinoconjunctivitis; and systemic anaphylaxis.

### III. NON-IGE-MEDIATED DISORDERS.

#### 1. Allergic Proctocolitis.

CP: Infants may present between 1 day and 3 mo of age with spots or streaks of blood and mucus in stool and occasional mild diarrhea.

Diagnosis: Increased numbers of white blood cells in stool and peripheral eosinophilia may be present.

Etiology: Most often, proctocolitis results from hypersensitivity to cow's milk; soy sensitivity is less common. This disorder also occurs in exclusively breast-fed patients and occasionally

Treatment: abates with maternal diet modification with elimination of milk products. Non-breast-fed infants can be treated with protein hydrolysate formulas. Occasionally, an amino acid-based formula may be required (NEOCATE<sup>R</sup>).

#### 2. Food-Induced Enterocolitis.

CP: Protracted vomiting and diarrhea begin between 1 wk and 3 mo of age.

Diagnosis:

- Stools contain occult blood, neutrophils, and eosinophils.
- Jejunal biopsy demonstrates flattened villi, edema, and inflammatory cells.
- Symptoms resolve within 72 hr of removal of the offending food and recur within 1–6 hr of reintroduction.

Treatment: Casein hydrolysate or amino acid-based formulas successfully treat most patients.

#### 3. Food-Induced Enteropathy.

CP: Malabsorption, protracted diarrhea, vomiting, and failure to thrive caused by food hypersensitivity occur most often in the 1st mo of life.

Dx: Small bowel biopsy shows patchy villus atrophy with mononuclear cell inflammatory response. Reaction to food challenge as well as resolution of symptoms on removal of the offending food may take several days to weeks.

#### 4. Celiac Disease (Gluten-Sensitive Enteropathy) and Dermatitis Herpetiformis.

Both entities occur as an immunologic response to gluten ingestion, and the two can occur together.

#### 5. Pulmonary Hemosiderosis (Heiner Syndrome).

Good Luck

# Critical care

## &

# toxicology

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## Hereditary Methemoglobinemia

### *Definition*

The iron in hemoglobin is normally in the ferrous state ( $Fe^{2+}$ ), which is essential for its oxygen-transporting function. Under physiologic conditions, there is a slow, constant loss of electrons to released oxygen and the ferric ( $Fe^{3+}$ ) form combines with water, producing methemoglobin (MHg).

An MHg level of 15% is associated with visible cyanosis; a level of 70% MHg is lethal. MHg may color the blood brown. Oxygen saturation will be low, but the arterial blood gas will show a normal or high (if receiving oxygen therapy)  $PaO_2$ .

### *Types*

#### I- Etiologies of Acquired Methemoglobinemia

##### MEDICATIONS

Benzocaine  
Chloroquine  
Dapsone  
Lidocaine  
Meloclopramide  
Nitrates  
Nitric oxide

##### MEDICAL CONDITIONS

Pediatric gastrointestinal infection, sepsis  
Sickle cell disease-related painful episode

##### MISCELLANEOUS

Herbicides/ Pesticides  
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)

#### II- HEREDITARY (DEFICIENCY OF NADH CYTOCHROME b5 REDUCTASE)

**Treatment** : ascorbic acid or methylene blue (IV 1-2 mg/kg oral 3-5 mg/kg/day).

## Pulmonary Edema

**Definition :** Pulmonary edema is an excessive accumulation of fluid in the interstitium and air spaces of the lung, resulting in oxygen desaturation and respiratory distress.

### Etiology of Pulmonary Edema

#### INCREASED PULMONARY CAPILLARY PRESSURE

Cardiogenic, such as left ventricular failure

Noncardiogenic, as in pulmonary veno-occlusive disease, pulmonary venous fibrosis, mediastinal tumors

#### INCREASED CAPILLARY PERMEABILITY

Bacterial and viral pneumonia

Acute respiratory distress syndrome (ARDS)

Vasoactive substances such as histamine, leukotrienes, thromboxanes

Diffuse capillary leak syndrome, as in sepsis

Uremia

#### LYMPHATIC INSUFFICIENCY

Congenital and acquired

#### DECREASED ONCOTIC PRESSURE

Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition

#### INCREASED NEGATIVE INTERSTITIAL PRESSURE

Upper airway obstructive lesions, such as croup and epiglottitis

#### MIXED OR UNKNOWN CAUSES

Neurogenic pulmonary edema

High-altitude pulmonary edema

Pancreatitis

Pulmonary embolism

#### Physical examination.

- Mechanism: Atelectasis and decreased surfactant production, resulting in decreased pulmonary compliance and decreased tidal volumes.
- Increased work of breathing in the form of tachypnea, dyspnea and frothy sputum.
- Fine crackles and wheezing, especially in dependent lung fields.
- In cardiogenic pulmonary edema, a gallop may be present as well as peripheral edema and jugular venous distension.



## Acetaminophen Toxicity

### Pathophysiology.

-Hepatic stores of glutathione are depleted to <70% of normal, the NAPQI metabolite can combine with hepatic macromolecules to produce hepatocellular damage.

-The acute toxic dose of acetaminophen is generally considered to be >200 mg/kg in children younger than 12 yr of age.

### Clinical and Laboratory Manifestations.

The plasma acetaminophen concentration should be plotted on the Rumack-Matthew nomogram to determine whether antidotal treatment is indicated.

### Classic Stages in the Clinical Course of Acetaminophen Toxicity

STAGE	TIME AFTER INGESTION	CHARACTERISTICS
I	0.5–24 hr	Anorexia, nausea, vomiting, malaise, pallor, diaphoresis
II	24–48 hr	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated bilirubin, prothrombin time, hepatic enzymes; oliguria.
III	72–96 hr	Peak liver function abnormalities; anorexia, nausea, vomiting, and malaise may reappear.
IV	4 days–2 wk	Resolution of hepatic dysfunction or complete liver failure.

### Treatment

-The antidote for acetaminophen poisoning is NAC (N-acetyl cysteine), which serves as a precursor for hepatic glutathione synthesis.

-NAC therapy is most effective when initiated early in the course of intoxication (within 8 hr), but may have value even if started 24–36 hr after the ingestion in severe cases.

- Oral NAC dose (140 mg NAC/kg oral loading dose 70 mg oral NAC/kg every 4 hr, for a total of 17 doses).
- For the IV formulation of NAC, an initial IV loading dose of 150 mg/kg is infused over 15–60 min, followed by an initial maintenance dose of 50 mg/kg infused over 4 hr, followed by 100 mg/kg infused over 16 hr
- Antiemetics (ondansetron) may be used to control vomiting.

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## SALICYLATES TOXICITY

### Pathophysiology(EFFECTS)

- Uncoupling oxidative phosphorylation.
- Inhibiting Krebs cycle enzymes.
- Inhibiting amino acid synthesis.
- Salicylates also decrease platelet adhesiveness.
- Increase pulmonary capillary permeability.

-The acute toxic dose of salicylates is generally considered  $>150$  mg/kg.

### Clinical and Laboratory Manifestations.

#### Acute salicylate ingestion

- o Nausea and vomiting occur due to gastric irritation.
- o Hyperventilation respiratory alkalosis with compensatory alkaluria.
- o Both potassium and sodium bicarbonate are excreted in the urine.
- o This "paradoxical aciduria" occurs in the presence of continued respiratory alkalosis.
- o Dehydration and progressive metabolic acidosis, caused by the accumulation of lactic acid and other metabolic acids, eventually develop.

#### Chronic salicylate poisoning

- Metabolic acidosis.
- Important signs of serious toxicity are CNS changes. (Agitation, restlessness, and confusion) are common in children.
- Coma may develop as a result of cerebral edema.
- Pulmonary edema or hemorrhage may develop in more severe cases.
- Hyperglycemia (acute) or hypoglycemia (chronic)
- Hepatotoxicity occurs after chronic exposure or with very large acute ingestions.
- Death results from pulmonary edema and respiratory failure, cerebral edema, hemorrhage, severe electrolyte imbalance, or cardiovascular collapse.
- Hyperpyrexia may also occur.

# Lead Poisoning

## *SOURCES OF EXPOSURE*

- Lead poisoning may occur in utero, because lead readily crosses the placenta from maternal blood.
- Several hundred products contain lead, including batteries, cable sheathing, cosmetics, mineral supplements, plastics, and toys
- The nonnutritive hand-to-mouth activity of young children is the most common pathway by which lead enters the body.

## *MECHANISM OF TOXICITY*

- ☒ It circulates bound to erythrocytes; about 97% is bound on or in the red blood cell.
- ☒ The accumulation of excess amounts of protoporphyrin and other heme precursors also is toxic.
- ☒ Erythrocyte protoporphyrin (EP) level is a useful tool for monitoring biochemical lead toxicity.
- ☒ A second mechanism of lead toxicity works via its competition with calcium.
- ☒ A third mechanism prevents the development of the normal tertiary brain structure.

## *CLINICAL SYMPTOMS*

- GI symptoms include (Anorexia, abdominal pain, vomiting, and constipation).
- CNS symptoms: due to increasing cerebral edema and increased intracranial pressure.
- (Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death)
- Renal tubular dysfunction is observed. Lead also may induce a reversible Fanconi.
- Red cell survival is shortened and may contribute to a hemolytic anemia.

## *DIAGNOSIS*

### SCREENING.

Screening by blood lead testing of all children at ages 12 mo and 24 mo was the standard in the U.S.

### INTERPRETATION OF BLOOD LEAD LEVELS.

A screening value at or above 10µg/dL requires repeat testing for a diagnosis and to determine the appropriate intervention. If venous BLL ≥ 45µg/dL, then prompt chelation therapy.

Follow-Up of Blood Lead Level Screening Test

IF SCREENING BLOOD LEAD LEVEL ( $\mu\text{g/dL}$ ) IS:	AAP REPEAT DIAGNOSTIC VENOUS BLOOD LEAD TESTING BY:
10-19	1 mo
20-44	1 wk
45-59	48 hr
60-69	48 hr
$\geq 70$	Immediately

OTHER TOOLS FOR ASSESSMENT.

- Blood lead level determinations remain the gold standard for evaluating lead poisoning.
- X-ray fluorescence (XRF).
- The Lead Mobilization Test.
- Radiographs of long bones may show dense bands at the metaphyses.
- KUB may reveal radiopaque flecks in the intestinal tract.

TREATMENT

The main components in the effort to eliminate lead poisoning are universally applicable to all children:

- (1) Identification and elimination of environmental sources of lead exposure;
- (2) Behavioral modification to reduce nonnutritive hand-to-mouth activity; and
- (3) Dietary counseling to ensure sufficient intake of the essential elements calcium and iron.

Drug treatment: A child with a venous BLL  $\geq 45 \mu\text{g/dL}$  should be treated.

## IRON TOXICITY

### *Pathophysiology.*

- Iron is corrosive to the gastrointestinal mucosa and may lead to intestinal ulceration, edema, and occasionally melena, hematemesis, and possibly perforation.
- It also accumulates in the mitochondria and tissues to produce cellular damage and systemic toxicity.
- Iron causes venodilation and increased capillary permeability, leading to hypotension.
- Early hypovolemia from intestinal losses, leading to lactic and citric acid accumulation, causing metabolic acidosis.
- Hepatic necrosis develops after serious poisoning, resulting in abnormal liver function test results and coagulopathies.
- Drowsiness and coma may develop as a result of hemodynamic instability or possibly as a direct toxic effect of iron in the CNS.

### *Clinical Manifestations.*

- ☒ Greater than 60 mg/kg of elemental iron is generally considered a toxic dose.
- ☒ Nausea, vomiting, diarrhea, and abdominal pain (usually develop within 30 min to 6 hr).
- ☒ Hematemesis and bloody diarrhea may develop in more serious poisonings.
- ☒ Gastric scarring, pyloric stenosis, and intestinal strictures can develop after 2–4 wk mucosa.

### *Diagnosis*

- ✦ Serum iron concentrations should be measured 4 hr after ingestion. Serum concentrations of >500 mg/dL indicate that significant toxicity is likely.
- ✦ AXR obtained to detect the radio-opaque iron tablets.
- ✦ Blood gas levels.
- ✦ The serum glucose concentration, liver function tests, and coagulation studies should be continuously monitored.

*Good luck*

# Infection

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## Meningitis

**Definition:** Meningitis implies primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement.

### Cerebrospinal Fluid Findings in Central Nervous System Disorders هام جدا

CONDITION	PRESSURE (MM H <sub>2</sub> O)	LEUKOCYTES (MM <sup>3</sup> )	PROTEIN (MG/DL)	GLUCOSE (MG/DL)	COMMENTS
Normal	50-80	<5, ≥75% lymphocytes	20-45	>50 (or 75% serum glucose)	

### COMMON FORMS OF MENINGITIS

Acute bacterial meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture.
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	Rarely >1,000 cells. PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF

## ETIOLOGY.

-The common pathogens include groups B and D streptococci (enterococcus), gram-negative enteric bacilli (*E. coli*, *Klebsiella*), and *Listeria monocytogenes*. Group B streptococcus followed by *E. coli* are the two most common causes of neonatal meningitis.

-In this same time frame, CNS infections caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b become increasingly prevalent.

### Risk factors

1. Lack of immunity to specific pathogens.
2. Recent colonization with pathogenic bacteria.
3. Close contact (household, daycare centers).
4. Specific host defense defects due to altered immunoglobulin production in response to encapsulated pathogens.
5. Defects of the complement system (C5-C8) have been associated with recurrent meningococcal infection.
6. Splenic dysfunction (sickle cell anemia) or asplenia (due to trauma, or congenital defect).
7. T-lymphocyte defects associated with an increased risk of *L. monocytogenes* infections of the CNS.
8. Congenital or acquired CSF leak across a mucocutaneous barrier.
9. Lumbosacral dermal sinus and meningomyelocele are associated with staphylococcal and gram-negative enteric bacterial meningitis.
10. CSF shunt infections increase the risk of meningitis due to staphylococci.

## CLINICAL MANIFESTATIONS.

- a) Nonspecific findings: include fever, anorexia and poor feeding, headache, symptoms of upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash.
- b) Meningeal irritation is manifested as nuchal rigidity, back pain, Kernig sign (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and Brudzinski sign (involuntary flexion of the knees and hips after passive flexion of the neck while supine).
- c) Increased ICP and Papilledema.
- d) Cranial neuropathies: ocular, oculomotor, abducens, facial, and auditory nerves.
- e) Seizures (focal or generalized) due to cerebritis, infarction, or electrolyte disturbances.
- f) Alterations of mental status



## Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

### VIRUSES

Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)  
 Herpes simplex (types 1,2)  
 Human herpesvirus type 6  
 Varicella-zoster virus  
 Epstein-Barr virus  
 Parvovirus B19  
 Cytomegalovirus  
 MMR  
 Influenza A and B  
 Parainfluenza

### BACTERIA

*Mycobacterium tuberculosis*  
*Leptospira* species (leptospirosis)  
*Treponema pallidum* (syphilis)  
*Borrelia* species (relapsing fever)  
*Bartonella* species (cat-scratch disease)  
*Rickettsia rickettsiae* (Rocky Mountain spotted fever)  
*Coxiella burnetii*  
*Mycoplasma pneumoniae*  
*Chlamydia trachomatis*  
*Chlamydia psittaci*  
*Chlamydia pneumoniae*

### BACTERIAL PARAMENINGEAL FOCUS

Sinusitis  
 Mastoiditis  
 Brain abscess

## Toxic shock syndrome

### Definition of Streptococcal Toxic Shock Syndrome

#### Clinical criteria

Hypotension plus 2 or more of the following:

- Renal impairment
- Coagulopathy
- Hepatic involvement
- Adult respiratory distress syndrome
- Generalized erythematous macular rash
- Soft tissue necrosis

#### Definite case

Clinical criteria plus group A streptococcus from a normally sterile site

#### Probable case

Clinical criteria plus group A streptococcus from a nonsterile site

#### DIAGNOSIS.

Same as APSGN.

#### TREATMENT.

- ⊗ Penicillin is the drug of choice(TARGOCID) or cephalosporins in allergic patients.
- ⊗ The antibiotics must be administered for the conventional 10 days.
- ⊗ IVIG(VIGAM)

## FEVER OF UNKNOWN ORIGIN

**DEFINITION:** The term fever of unknown origin (FUO) is best reserved for children with a fever documented by a health care provider and for which the cause could not be identified after 3 wk of evaluation as an outpatient or after 1 wk of evaluation in hospital.

### ETIOLOGY.

1. Abscesses: abdominal, brain, dental, hepatic, pelvic

2. Infections

Bacteria

Actinomycosis

Brucellosis

*Campylobacter*

*Listeria monocytogenes* (Listeriosis)

Meningococcemia (chronic)

*Mycoplasma pneumoniae*

*Salmonella*

Tuberculosis

Localized infections

Cholangitis

Infective endocarditis

Mastoiditis

Osteomyelitis

Pneumonia

Pyelonephritis

Sinusitis

Spirochetes

*Borrelia burgdorferi* (Lyme disease)

Syphilis

Fungal diseases

Blastomycosis (extrapulmonary)

Coccidioidomycosis (disseminated)

Histoplasmosis (disseminated)

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## DIAGNOSIS.

### History.

1. Age:
  - Children <6 yr of age often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JRA.
  - Adolescent patients are more likely to have tuberculosis, inflammatory bowel disease, autoimmune processes, or lymphoma, in addition to the causes of FUO found in younger children.
2. A history of exposure to wild or domestic animals :leptospires
3. A history of ingestion of rabbit :tularemia.
4. A history of tick bite :rocky mountain spotted fever.
5. Any history of pica should :*Toxocara* or *Toxoplasma gondii* (toxoplasmosis).
6. A history of travel to endemic area: Malaria, histoplasmosis, and coccidioidomycosis
7. A medication history: eye drops( atropine-induced fever).
8. The genetic background :nephrogenic diabetes insipidus and Familial dysautonomia .
9. Ancestry from the Mediterranean should suggest the possibility of familial Mediterranean fever (FMF).

### Physical Examination.

- a) Sweating : absence of sweat in the presence of an elevated body temperature suggests dehydration, familial dysautonomia, or exposure to atropine.
- b) A careful ophthalmic examination:
  - o Conjunctivitis: polyarteritis nodosa , measles, coxsackievirus , Kawasaki disease and infective endocarditis.
  - o Uveitis suggests sarcoidosis, JRA, systemic lupus erythematosus, Kawasaki disease, Behçet disease, and vasculitis.
  - o Chorioretinitis suggests CMV, toxoplasmosis, and syphilis.
  - o Proptosis suggests orbital tumor, thyrotoxicosis and (neuroblastoma).
  - o Nailfold capillary abnormalities :Juvenile dermatomyositis and systemic scleroderma.
  - o Failure of pupillary constriction: hypothalamic dysfunction.
  - o lack of tears & an absent corneal reflex: familial dysautonomia.
- C) Tenderness to tapping over the sinuses : sinusitis.
- D) Oral exam.: oral candidiasis .
- E) Fever blisters : pneumococcal , streptococcal infection & meningococcal meningitis.
- F) Hyperemia of the pharynx: infectious mononucleosis & Kawasaki disease.

## Enteric Fever (Typhoid Fever)

### ETIOLOGY.

Typhoid fever is caused by *Salmonella Typhi* (S. Typhi), a gram-negative bacterium. A very similar but often less severe disease is caused by S. Paratyphi A and rarely by S. Paratyphi B and S. Paratyphi C.

### PATHOGENESIS.

The disease occurs by the ingestion of the organism (feco-oral). The incubation period of typhoid fever is usually 7–14 days

### CLINICAL FEATURES.

Typhoid fever usually presents with

- High-grade fever.
- Generalized myalgia.
- Hepatosplenomegaly.
- Abdominal pain.
- Anorexia.
- In about 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7th–10th day of the illness, and lesions may appear in crops of 10–15 on the lower chest and abdomen and last 2–3 days.

### Extraintestinal Infections Complications of Typhoid Fever Caused by *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM INVOLVED	COMPLICATIONS
Central nervous system	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	Pneumonia, empyema, bronchopleural fistula
Bone and joint	Osteomyelitis, septic arthritis
Hepatobiliary system	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue infections	Psoas abscess, gluteal abscess, cutaneous vasculitis
Haematologic	Haemophagocytosis syndrome

» Vaccinations:

- An oral, live-attenuated preparation of the Ty21a strain of *S. Typhi* has been shown to have good efficacy (67–82%) for up to 5 years.
- The Vi capsular polysaccharide can be used in people  $\geq 2$  yr of age. It is given as a single intramuscular dose, with a booster every 2 yr and has a protective efficacy of 70–80.
- The recent Vi-conjugate vaccine has been shown to have a protective efficacy exceeding 90% .

## Parvovirus B19

Parvovirus B19 is the cause of erythema infectiosum or "fifth disease," 1 of the classic childhood exanthems.

### ETIOLOGY.

Parvovirus B19 (B19) is a member of Parvoviridae. Parvoviruses are small DNA viruses.

### EPIDEMIOLOGY.

- Infections with parvovirus B19 are most prevalent in school-aged children.
- Transmission of B19 is by the respiratory route and blood products.

### PATHOGENESIS.

The primary target of B19 infection is the erythroid cell line, specifically erythroid precursors leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis.

### CLINICAL MANIFESTATIONS.

#### 1. Erythema Infectiosum (Fifth Disease).

Which is a benign, self-limited exanthematous illness of childhood. The incubation period for erythema infectiosum is 4–28 days (average 16–17 days).

The prodromal phase is mild and consists of low-grade fever, headache, and symptoms of mild upper respiratory tract infection.

#### The exanthema phase:

- The initial stage is an erythematous facial flushing, often described as a "slapped-cheek" appearance.
- The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema.
- Central clearing of macular lesions occurs promptly. The rash tends to be more prominent on extensor surfaces, sparing the palms and soles.
- Affected children are afebrile and not ill appearing.
- The rash resolves spontaneously without desquamation.

#### 2. Arthropathy.

The joint symptoms are self-limited and, in the majority of patients, resolve within 2–4 wk.

# Polioviruses

## ETIOLOGY.

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae.

## Transmission.

It spreads by the fecal-oral route.

## CLINICAL MANIFESTATIONS.

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8–12 days.

### I. Abortive Poliomyelitis.

In about 5% of patients, a nonspecific influenza-like syndrome (FAHM) occurs 1–2 wk after infection, which is termed abortive poliomyelitis.

### II. Nonparalytic Poliomyelitis.

- More intense headache, nausea, and vomiting.
- Soreness and stiffness of the posterior muscles of the neck, trunk, and limbs.
- Fleeting paralysis of the bladder and constipation are frequent.
- Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes.

### III. Paralytic Poliomyelitis.

Paralytic poliomyelitis develops in about 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes: (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) poliomyelitis.

#### A. Spinal paralytic poliomyelitis :

- Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop.
- In the spinal form there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities.
- Sensation is intact.



*Good Luck*

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## Non-GERD Esophagitis

### 1. Eosinophilic esophagitis

- Definition: The esophageal epithelium is infiltrated by eosinophils, typically in a density exceeding 15 per high power field. Little is known about its natural history.
- Clinical manifestations: The mean age at diagnosis is 7 yr (range 1-17 yr) with the duration of symptoms of 3 yr. Vomiting, chest or abdominal pain, and dysphagia with occasional food impactions or strictures are the main manifestations. Patients often have atopy, or food allergies.

Diagnosis: Peripheral eosinophilia (~50% of patients), elevated IgE levels, endoscopy revealed a granular, furrowed, or ringed appearance and esophageal histology reveals eosinophilic infiltrates.

DD: GERD. Eosinophilic esophagitis is characterized by its general lack of erosive esophagitis, greater eosinophil density, and its refractoriness to antireflux therapies.

Complication: Stricture formation.

Treatment: Elimination diets for those with proven allergies + inhaled and systemic corticosteroids. Therapies under investigations include leukotriene inhibitors (montelukast) and anti-interleukin 5 antibody (mepolizumab).

2. Infective esophagitis: Uncommon and most often affecting immunocompromised children, but may affect immunocompetent.

Clinical manifestations: include odynophagia, dysphagia, and retrosternal pain; there may also be fever, nausea, and vomiting. The infective esophagitis may progress to esophageal stricture.

Diagnosis: It is made by endoscopy and histopathologic examination of biopsy; adding PCR, tissue viral culture, and immunocytochemistry enhances the diagnostic sensitivity.

Treatment: Antimicrobial agents, analgesics, and antacids.

a. Esophageal candidiasis: It usually occurs in immunosuppressed hosts receiving chemotherapy for hematologic or neoplastic diseases. Oral moniliasis may be absent.

Treatment: a. Itraconazole 2-6 mg/kg/day orally.

b. Amphotericin and/or flucytosine are used in systemic infection and resistant cases.

c. Stop antibiotics (if possible).

Prognosis: It is related to that of the underlying disease.

b. Bacterial esophagitis

\* Diphtheria: Extension of the membrane from the oropharynx.

\* Tuberculosis: Extension from the larynx or a tubercular lymph node.

\* Other bacteria: They may invade esophageal mucosa in immunocompromised hosts.

c. Viral esophagitis: It is caused by herpes simplex, CMV, and occasionally varicella zoster. Vesicular lesions in the pharynx and endoscopy demonstrate the same lesions in the esophagus.

Treatment: Viscous 2% lidocaine 2-3 mL every 4 hr leads to symptomatic relief.

Acyclovir is indicated in immunosuppressed patients, 750 mg/m<sup>2</sup>/24 hr in 3 doses for herpes and varicella infection (foscarnet is used in HSV resistant to acyclovir).

Ganciclovir 10 mg/kg/24 hr in 2 divided IV doses for CMV infection.

3. "Pill" esophagitis: These acute injuries are produced by contact with a damaging agent. Medications implicated in "pill" esophagitis include tetracycline, potassium chloride, ferrous sulfate, and nonsteroidal anti-inflammatory medications, with the tablet most often ingested at bedtime with inadequate water. Clinical manifestations: Progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy: A focal lesion often localized to one of the upper or middle regions of the esophagus.

## Clinical picture of celiac disease

Active Childhood Celiac Disease: INTESTINAL

### SYMPTOMS

Failure to thrive

Diarrhea

Irritability

Vomiting

Anorexia

Foul stools

Abdominal pain

Excessive appetite

Rectal prolapse

### SIGNS

Height <25th percentile

Body weight <25th percentile

Wasted muscles

Abdominal distention

Edema

Finger clubbing

## HELICOBACTER PYLORI GASTRITIS.

### ETIOLOGY

*H. pylori* is a gram-negative, S-shaped rod that produces urease, catalase, and oxidase, which may play a role in the pathogenesis of peptic ulcer disease. It is responsible for most cases of erosive gastritis.

### RISK FACTORS AND MODE OF TRANSMISSION

The mechanism of acquisition and transmission: fecal-oral or oral-oral.

Risk factors such as low socioeconomic status.

### CLINICAL PICTURE

- a) All children develop histologic chronic active gastritis but are often asymptomatic.
- b) In children, *H. pylori* infection can present with abdominal pain or vomiting.
- c) Refractory iron deficiency anemia or growth retardation.
- d) Chronic autoimmune thrombocytopenia.
- e) Chronic colonization with *H. pylori* can predispose children to a duodenal ulcer, gastric cancer such as adenocarcinoma, or MALT (mucosa-associated lymphoid tissue) lymphomas.

### DIAGNOSIS

- Gastric biopsies should always be obtained from the body and antrum of the stomach.
- Endoscopic findings varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity, or ulcers
- Immunoglobulin G (IgG) antibody :for screening children for the presence of *H. pylori*, but not to predict active infection or assess the success of antimicrobial therapy.
- <sup>13</sup>C-urea breath tests.
- Rapid urease test.
- Stool antigen tests

## Pseudomembranous Colitis (Clostridium Difficile)

**Definition:** Clostridium difficile-associated diarrhoea, also known as antibiotic-associated diarrhea or pseudomembranous colitis.

### ETIOLOGY.

C. difficile is spore-forming, gram-positive, anaerobic bacillus. The organism produces 2 toxins:

- Toxin A (enterotoxin) acts on the intestinal mucosa to produce diarrhea.
- Toxin B (cytotoxin) increases vascular permeability in low doses and is lethal to experimental animals in high doses.

### RISK FACTORS

- a) C. difficile-associated diarrhea occurs in the setting of altered bowel flora, which is most commonly due to antimicrobial therapy. Ampicillin, 2nd and 3rd generation cephalosporins, and clindamycin.
- b) Gastrointestinal surgery and chemotherapy are additional risk factors. The risk for disease increases with enteral feedings, especially if the feedings bypass the stomach. Normal gastric acidity destroys the spores of C. difficile.

### PATHOGENESIS.

Both toxins are internalized and act within cells to modify proteins, resulting in cell death. Inflammatory response contributes to the diarrhea and formation of pseudomembranes.

### CLINICAL MANIFESTATIONS. (4 clinical pictures)

- Asymptomatic colonization is common in infants and young children.
- A mild self-limited diarrhea without pseudomembranes.
- Explosive watery diarrhea with occult blood.
- Pseudomembranous colitis with bloody diarrhea accompanied by fever, cramps, abdominal pain, nausea, and vomiting.

### DIAGNOSIS.

- Detecting C. difficile or its toxin in the stool.
- Enzyme immunoassay tests (ELISA) that detect toxin A only, or toxin A plus B.
- Sigmoidoscopy or colonoscopy : pseudomembranous nodules and plaques.
- Fecal leukocytes are present in approximately half of cases.
- Occult or frank blood is common.

### TREATMENT.

- ⊗ The 1st and essential step in treatment is the discontinuation of the current antibiotics.
- ⊗ If symptoms persist, antibiotics cannot be discontinued, or the illness is severe, then oral metronidazole (20–40 mg/kg/day divided every 6–8 hr PO) or oral vancomycin (25–40 mg/kg/day divided every 6 hr PO) should be given for 7–10 days.
- ⊗ Nitazoxanide has been effective in adults with C. difficile colitis.
- ⊗ Contact isolation of patients is critical to avoid nosocomial spread.

## Acute Pancreatitis

### Etiology of Acute Pancreatitis in Children

#### DRUGS AND TOXINS

Acetaminophen overdose

Alcohol

Azathioprine

Cimetidine

Corticosteroids

Enalapril

Erythromycin

#### INFECTIOUS

Malaria

Measles/Mumps/Rubella

Mycoplasma

Septic shock

#### OBSTRUCTIVE

Choledochal cyst

Choledocholithiasis (stones or sludge)

Sphincter of Oddi dysfunction

Tumor

#### SYSTEMIC DISEASE

$\alpha_1$ -antitrypsin deficiency

Crohn disease

Cystic fibrosis

Diabetes mellitus

Hemochromatosis

Hemolytic uremic syndrome

Hyperlipidemia: type I, IV, V

Hyperparathyroidism/Hypercalcemia

#### TRAUMATIC

Blunt injury/Burns

## PATHOGENESIS

- a) Trypsinogen is activated to trypsin, which then activates other pancreatic proenzymes, leading to autodigestion.
- b) Release of cytokines and subsequent depletion of antioxidants leads to pancreastasis and the further activation of pancreatic proenzymes.

## CLINICAL MANIFESTATIONS.

- The pain is epigastric or in either upper quadrant and steady with antalgic position.
- The child is very uncomfortable and irritable and appears acutely ill.
- Persistent vomiting and fever.
- The abdomen may be distended and tender. A mass may be palpable. The pain increases in intensity for 24–48 hr, severe abdominal pain.
- *Severe acute pancreatitis*: In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (*Cullen sign*) or in the flanks (*Grey Turner sign*). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass.

## DIAGNOSIS.

- Measurement of serum amylase (lasts for 4 days) and lipase (lasts for 2wks) activities.
- CBC and electrolytes: hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated  $\gamma$ -glutamyl transpeptidase, and hyperbilirubinemia.
- CXR: atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left-(rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema.
- AXR may demonstrate a sentinel loop, dilatation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.
- Ultrasound and, more specifically, CT scanning reveal pancreatic enlargement, a hypoechoic, sonolucent edematous pancreas, pancreatic masses, fluid collections, and abscesses.
- Endoscopic retrograde cholangiopancreatography (ERCP) and *magnetic resonance cholangiopancreatography (MRCP)*.



## Extraintestinal Manifestations of Enteric Infections(gastroenteritis)

MANIFESTATION	ASSOCIATED ENTERIC PATHOGEN(S)	ONSET AND PROGNOSIS
<u>Focal infections</u> due to systemic spread of bacterial pathogens, including vulvovaginitis, urinary tract infection, endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft tissue infection, and septic thrombophlebitis	All major pathogens can cause such direct extraintestinal infections, including <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i>	Onset usually during the acute infection, but may present subsequently. Prognosis depends on infection site.
<u>Reactive arthritis</u>	<i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Cryptosporidium</i> , <i>Clostridium difficile</i>	Typically occurs about 1–3 wk after infection. Relapses after reinfection may develop in 15–50% of people but most children recover fully within 2–6 mo after the 1st symptoms appear.
<u>Guillain-Barré syndrome</u>	<i>Campylobacter</i>	Usually occurs a few weeks after the original infection. Prognosis good although 15–20% may have sequelae.
<u>Glomerulonephritis</u>	<i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i>	Can be of sudden onset in acute, referring to a sudden attack of inflammation, or chronic, which comes on gradually. In most cases, the kidneys heal with time.
<u>IgA nephropathy</u>	<i>Campylobacter</i>	Characterized by recurrent episodes of blood in the urine, this condition results from deposits of the protein immunoglobulin A (IgA) in the glomeruli. IgA nephropathy can progress for years with no noticeable symptoms. Men seem more likely to develop this disorder than are women.
<u>Erythema nodosum</u>	<i>Yersinia</i> , <i>Campylobacter</i> , <i>Salmonella</i>	Although painful, is usually benign and more commonly seen in adolescents. Resolves with 4–6 weeks.

*Good luck*

# Hepatology

IMAD ATTIA  
2013

# ASCITES

**Definition:** The term ascites indicates an accumulation of fluid in the peritoneal cavity. It is usually applied to accumulation of serous fluid.

## Etiology

TABLE 32. Causes of Ascites

<p><b>1 Hepatic</b></p> <ul style="list-style-type: none"> <li>• Cirrhosis</li> <li>• Congenital hepatic fibrosis</li> <li>• Portal vein obstruction</li> <li>• Fulminant hepatic failure</li> <li>• Budd-Chiari syndrome</li> <li>• Lysosomal storage disease</li> </ul> <p><b>2 Renal</b></p> <ul style="list-style-type: none"> <li>• Nephrotic syndrome</li> <li>• Obstructive uropathy</li> <li>• Perforation of urinary tract</li> <li>• Peritoneal dialysis</li> </ul> <p><b>3 Cardiac</b></p> <ul style="list-style-type: none"> <li>• Heart failure</li> <li>• Constrictive pericarditis</li> </ul>	<p><b>4 Infectious</b></p> <ul style="list-style-type: none"> <li>• Abscess</li> <li>• Tuberculosis</li> <li>• Chlamydia</li> <li>• Schistosomiasis</li> </ul> <p><b>5 Gastrointestinal</b></p> <ul style="list-style-type: none"> <li>• Infarcted bowel</li> <li>• Perforation</li> </ul> <p><b>6 Neoplastic</b></p> <ul style="list-style-type: none"> <li>• Lymphoma</li> <li>• Neuroblastoma</li> </ul> <p><b>7 Gynecologic</b></p> <ul style="list-style-type: none"> <li>• Ovarian tumors</li> <li>• Ovarian torsion, rupture</li> </ul>	<p><b>8 Pancreatic</b></p> <ul style="list-style-type: none"> <li>• Pancreatitis</li> <li>• Ruptured pancreatic duct</li> </ul> <p><b>9 Miscellaneous</b></p> <ul style="list-style-type: none"> <li>• Systemic lupus erythematosus</li> <li>• Ventriculoperitoneal shunt</li> <li>• Eosinophilic ascites</li> <li>• Chylous ascites</li> <li>• Hypothyroidism</li> </ul> <p><b>10 Biliary ascites</b></p>
--	--	--

## Causes of Fetal and Neonatal Ascites

As part of hydrops fetalis (generalized edema)

1. Immune.

2. Non immune (for causes, see Postgraduate Neonatology).

Ascites with minimal peripheral edema.

Viscus rupture

(a) Urinary (obstructive uropathy): It is the commonest cause.

(b) Gut (meconium peritonitis).

(c) Biliary.

(d) Ovarian cyst.

3. Lysosomal storage diseases: GM1 gangliosidosis, sialidosis, mucopolysaccharidoses, Gaucher's disease, Wolman's disease, and Niemann-Pick type C.

4. Hepatic:  $\alpha_1$ -antitrypsin deficiency, Budd-chiari syndrome, congenital hepatic fibrosis, and intrauterine infections.

5. Short-limbed dwarfisms: Chondrodysplasia punctata (conradi's), Achondroplasia, and Thanatophoric dwarfism.

6. Chylous: Congenital anomaly of the thoracic duct.

7. Transient fetal ascites.

Anemia, G6PD,  $\alpha$ -thalassaemia  
SUT (AF) (G6PD) black  
encephalopathy  
T. rubrum  
To RCH

Neonatal

## Drug- and Toxin- Induced Liver Injury

Phase 1 → Reductase  
Hydrolase  
Phase 2 → transferase  
enzyme  
Phase 3 → energy dependent  
carrier

### Hepatic metabolism of drugs and toxins

The major initial step in drug metabolism (phase 1) utilizes two classes of enzymes, oxidoreductases (cytochrome P450 system, amine oxidases, aldo/keto-reductase, azo-reductase), and hydrolases (esterases, epoxide-hydrolase) which generate reactive products from the parent compound as they introduce carboxyl, epoxide, or hydroxyl groups. These chemical groups serve as acceptors of glucuronic acid, sulphates, glutathione acetate, and amino acids in reactions catalysed by a series of transferases (phase 2). Many compounds can be metabolized by phase 2 reactions without undergoing a phase 1 reaction. The end product of metabolism is usually a water soluble product which will be excreted in the urine and/or the bile. (Phase 3) is the energy-dependent excretion of drug metabolites by membrane transporters.

Impaired drug metabolism via phase 1 and 2 reactions present in the first few months of life is followed by a period of enhanced metabolism of many drugs in children through 10 yr of age compared with adults.

### Classification of chemical hepatotoxicity

1. Predictable hepatotoxicity with dose dependency (frequent): The injury is proportional with the dose and duration of administration, occurring within days of starting the drug and can be reproduced in man and experimental animals and the drug can be detected in tissues or body fluids.

A. Direct injury: Through alteration of membrane lipids or through denaturation of proteins.

Examples: Carbon tetrachloride and trichloroethylene.

B. Indirect injury:

a. Cytotoxic: Through interference with metabolic pathways essential for cell integrity.

Examples: Acetaminophen, paracetamol, and antimetabolites such as methotrexate or 6-mercaptopurine.

b. Cholestatic: Through interference with bile excretory mechanisms.

Examples: Anabolic steroids, methyl testosterone, and chlorpromazine & cytharabine.

2. Idiosyncratic hepatotoxicity: Infrequent and unpredictable injury. The injury is not dose-dependent and may occur at any time during exposure to the agent.

A. Immunologically-mediated hepatotoxicity: The drug or one of its metabolites may change cell membranes so that they become immunoreactive → autoimmune mechanisms.

Duration of exposure before reaction is generally 1-4 wk. The hepatocellular damage may occur with features of generalized hypersensitivity (fever, rash, arthralgia, and eosinophilia).

Examples: Methyl dopa and anticonvulsants (phenytoin, phenobarbital, carbamazepine).

B. Aberrant pathways for drug metabolism with the production of toxic intermediates.

The duration of drug usage prior to liver injury is variable (weeks to 1 yr or more).

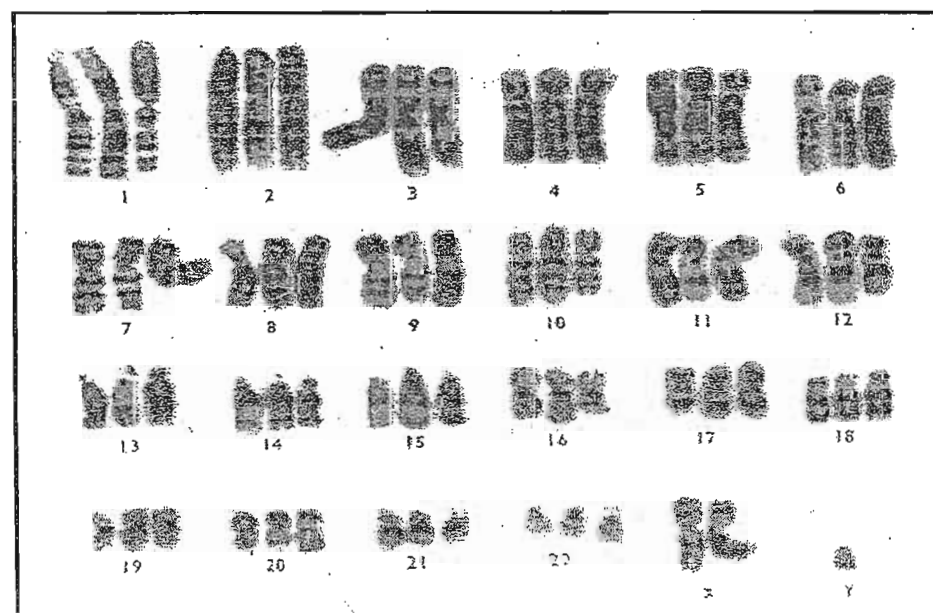
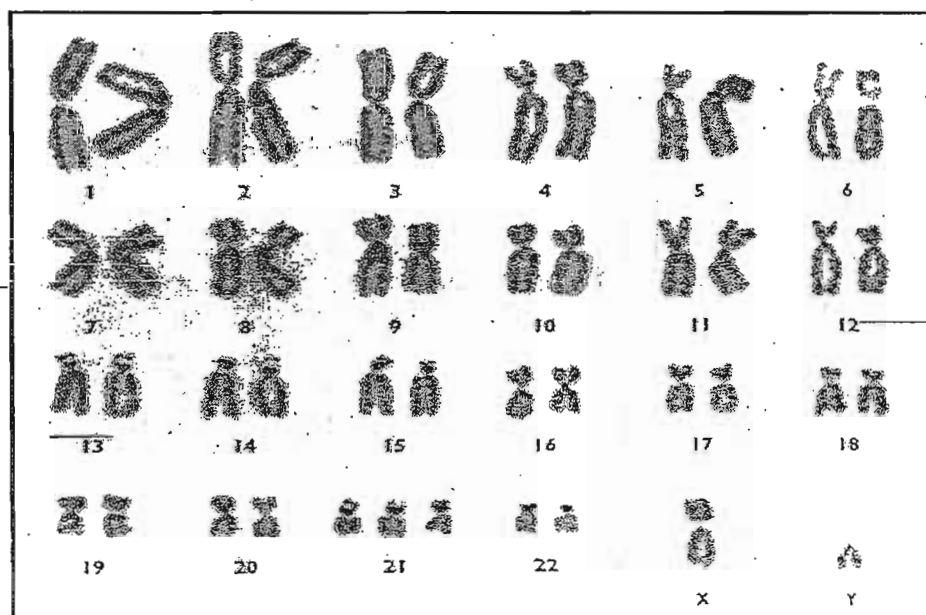
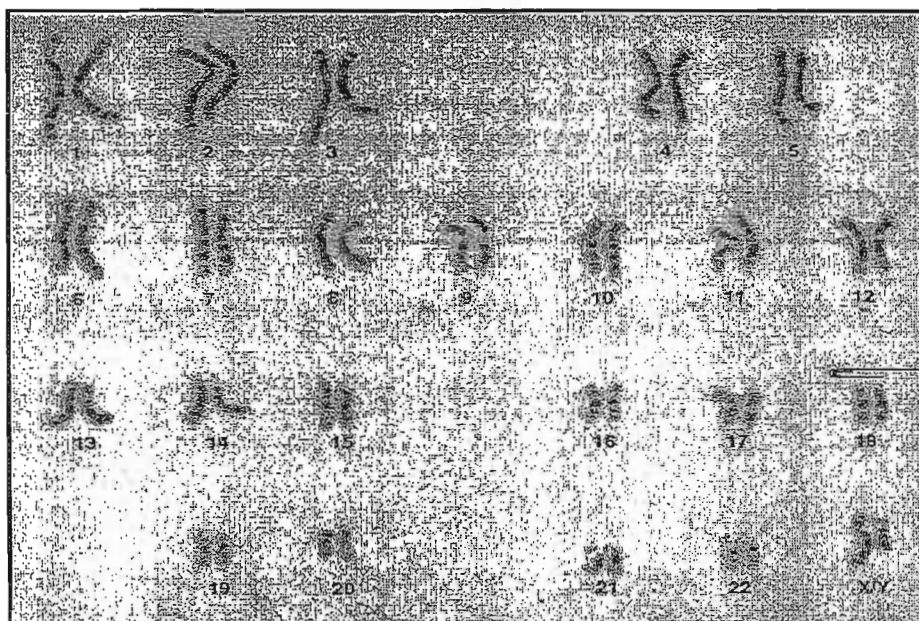
Examples: Isoniazid and sodium valproate.

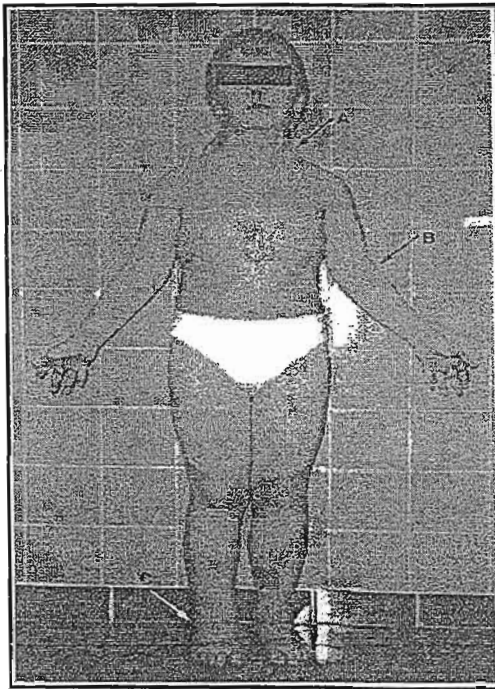
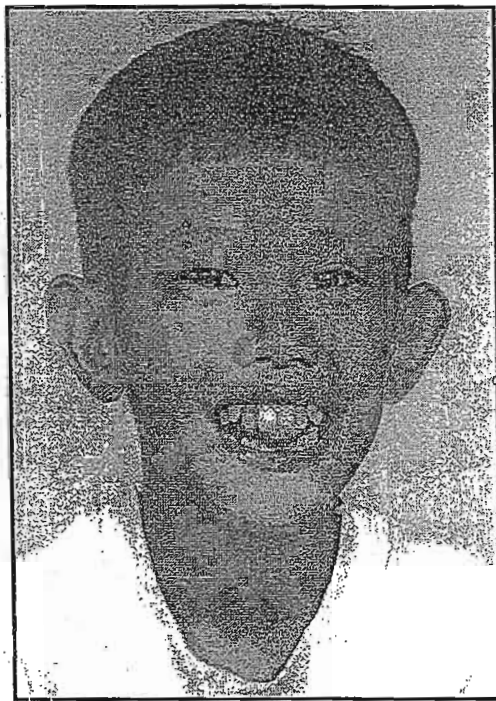
### Clinical manifestations

Symptoms: Fever, malaise, rash, and arthralgia.

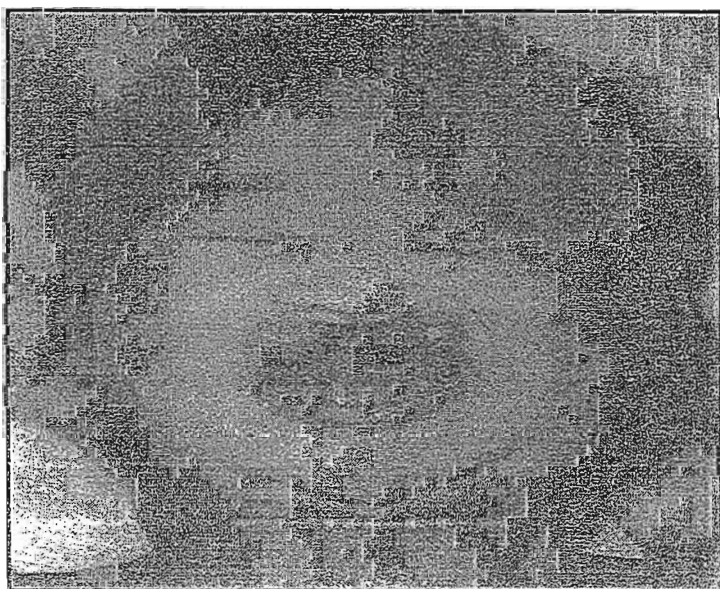
Signs: Signs of liver dysfunction. PT/PTT may be a complication.

**Medical Genetics**  
**By**  
**Ahmed M.Badr ( MD)**  
**Lecturer of pediatrics**  
**Cairo University**  
**2012**

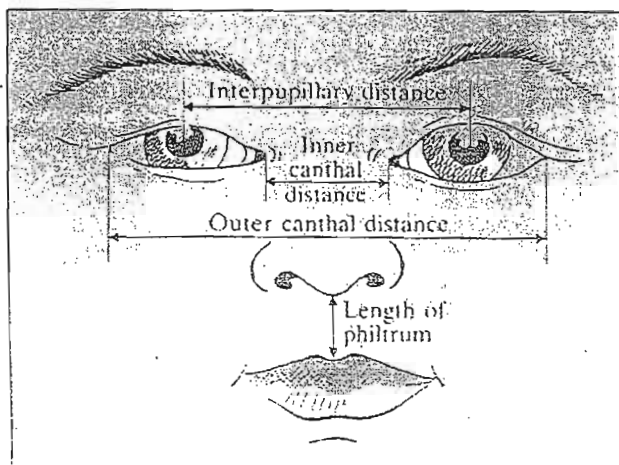
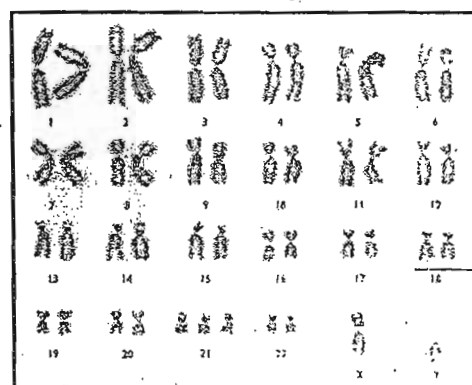
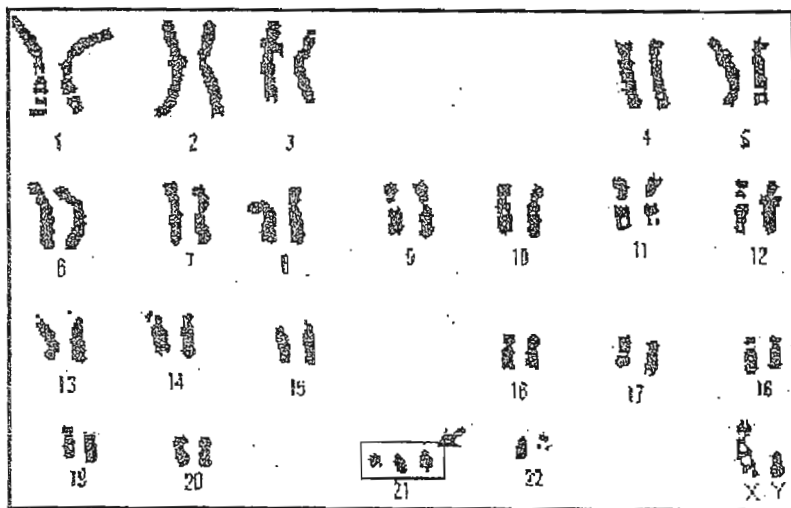
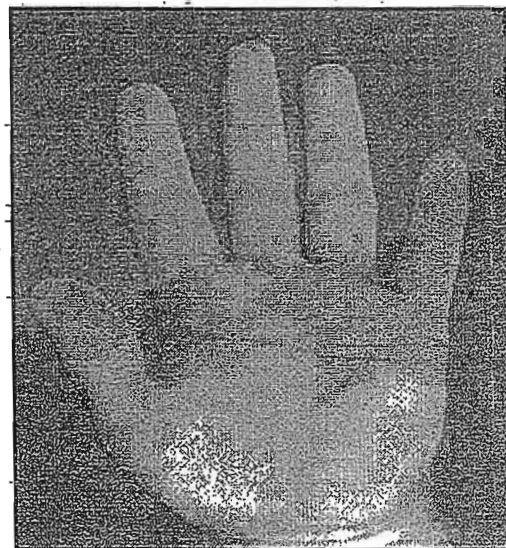


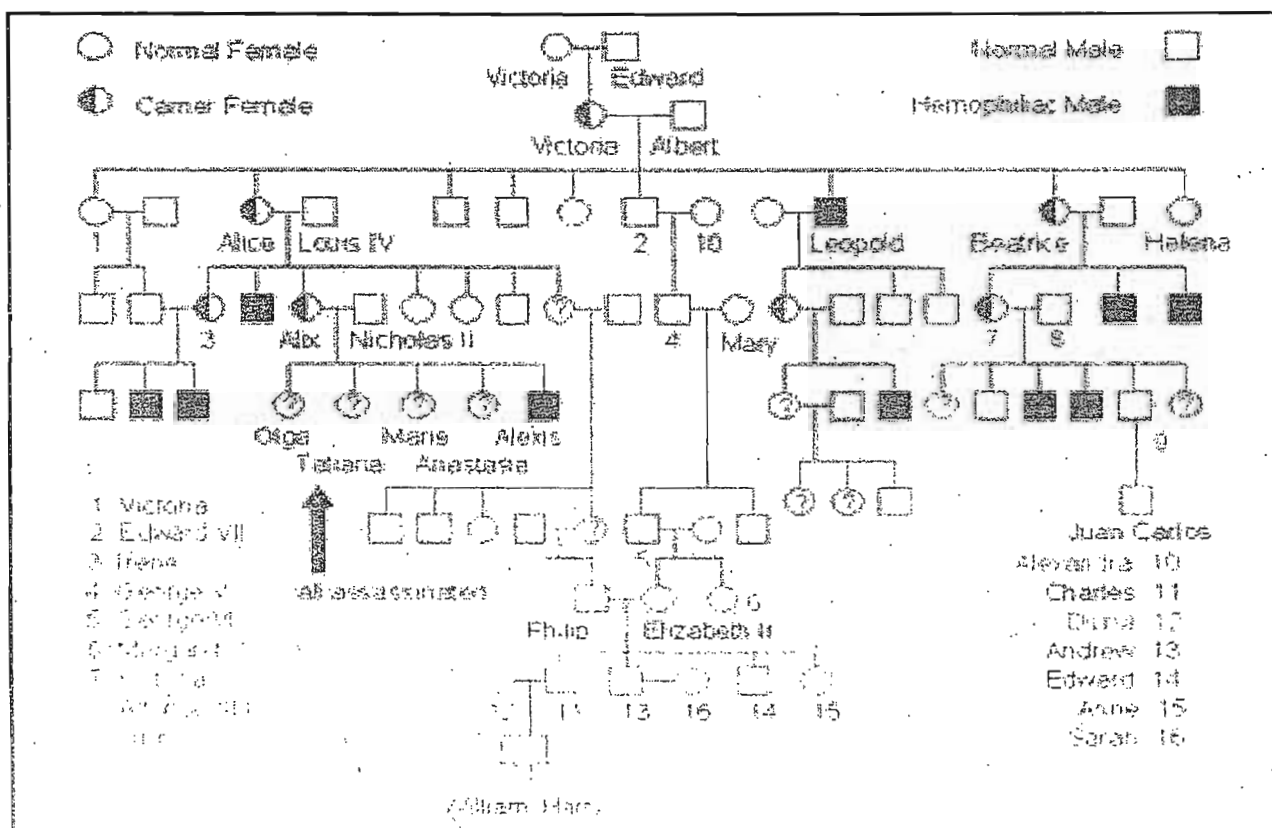
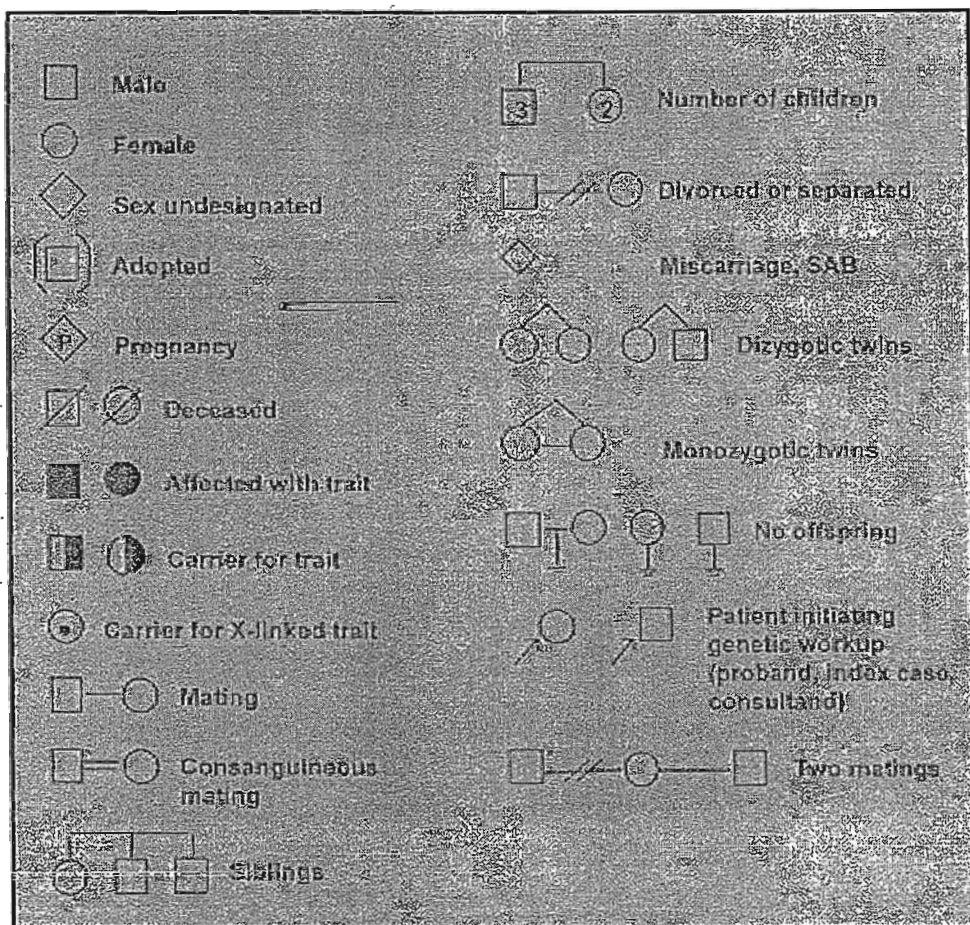


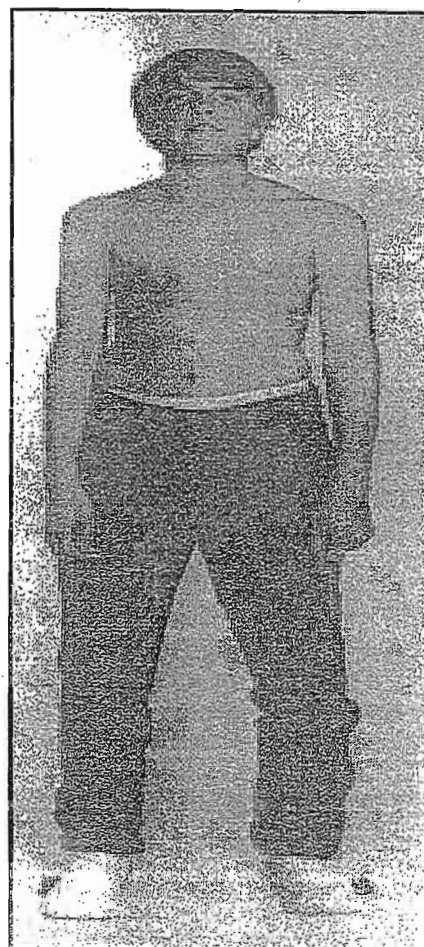
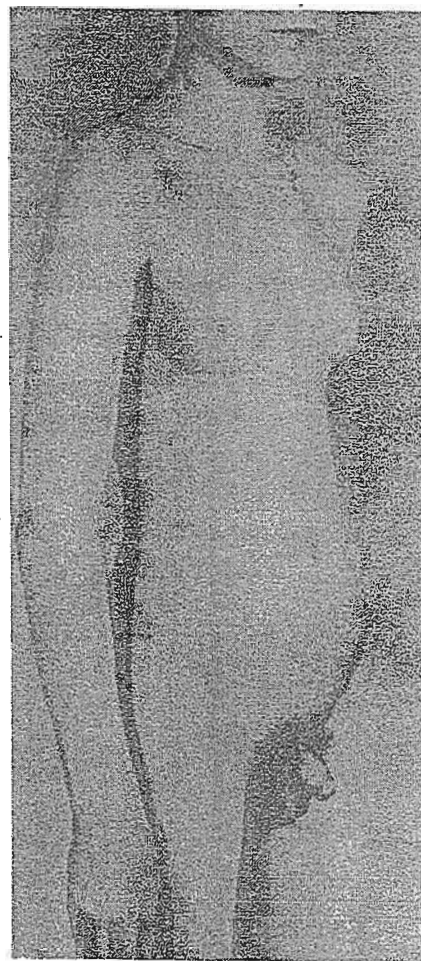
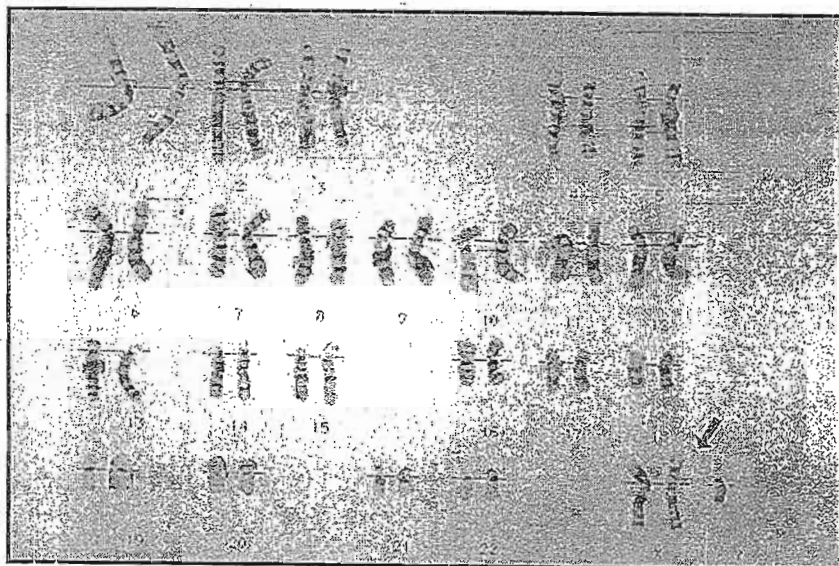


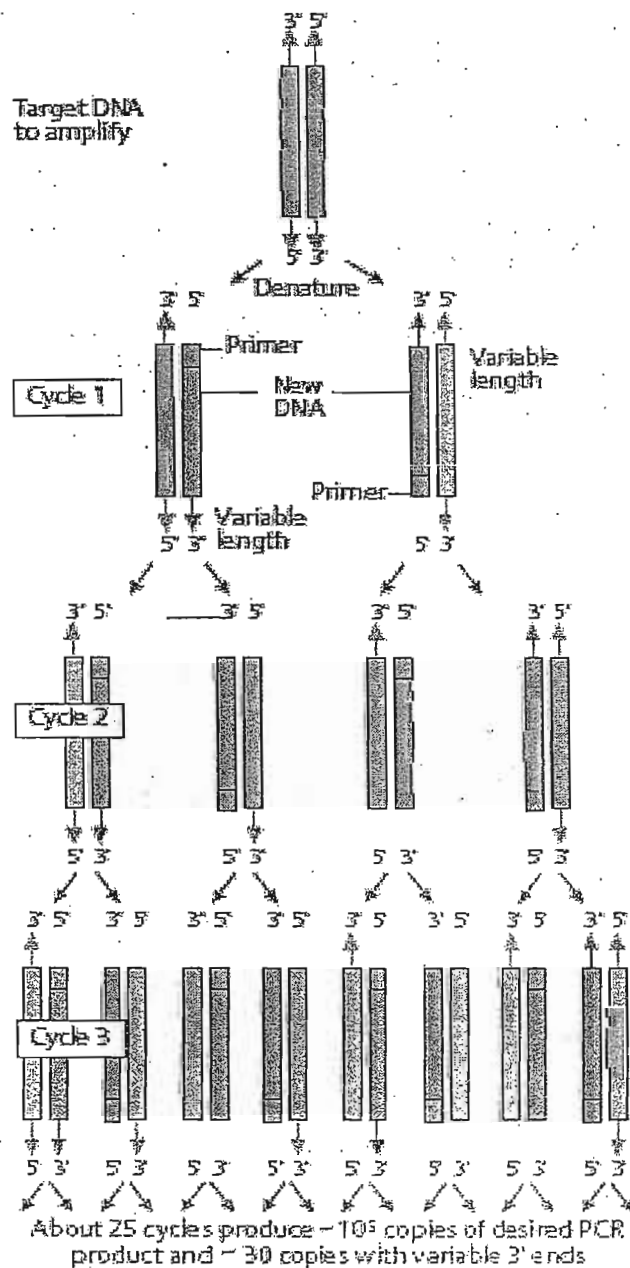
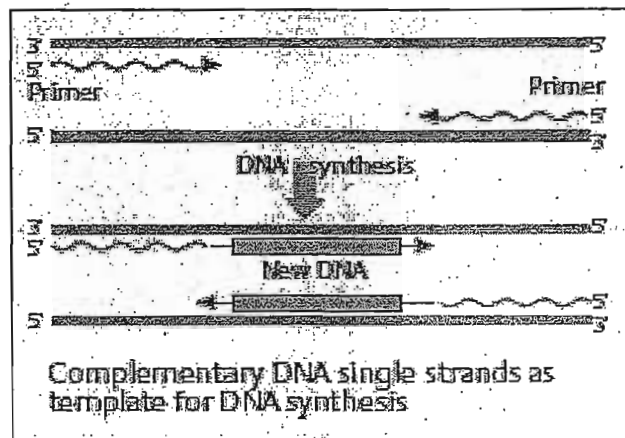












A. Polymerase chain reaction (PCR)



# Cell Structure

The cell is formed of:

## A) Nucleus:

- ☒ Nuclear membrane
- ☒ Nucleolus
- ☒ Nuclear matrix
- ☒ Chromatin: During cell division, chromatin is *condensed* into separate chromosomes

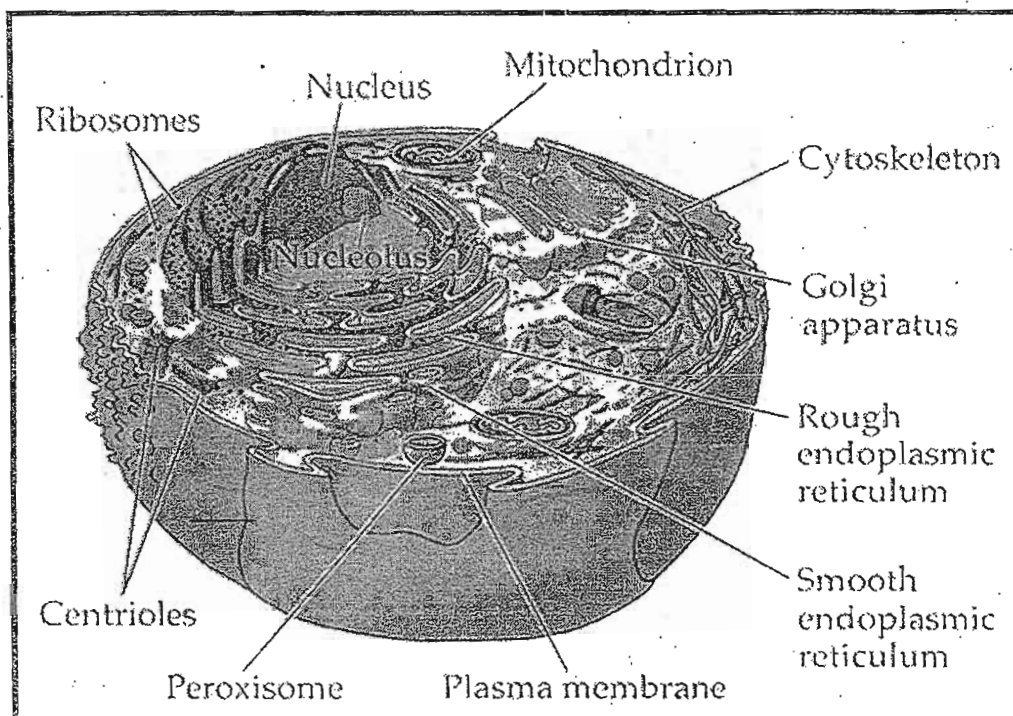
### Remember

All cells have nuclei except RBCs

## B) Cytoplasm: Contains the following organelles

- ☒ Endoplasmic reticulum "Transport"
- ☒ Golgi apparatus "Protein synthesis"
- ☒ Mitochondria "Energy production"
- ☒ Ribosomes "Protein synthesis"
- ☒ Peroxisomes "Fatty acid metabolism"

The total length of all DNA strands = 2 meters



# Human Chromosomes

## Definition

Thread-like structures found in the nucleus and formed of:

- a. **DNA** (Deoxyribonucleic acid): carries the genetic information (Genes)
- b. **Proteins** [Histones & non-histones]: responsible for DNA coiling (Packing)

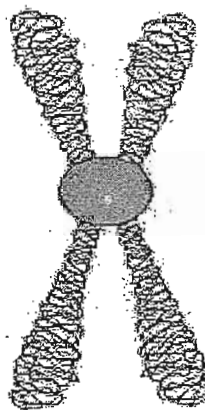
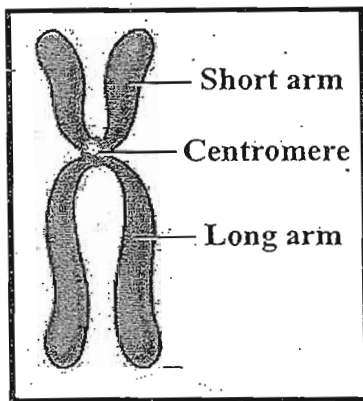
## Number

- o Each **somatic** cell contains 46 chromosomes (23 pairs =  $2n$  = diploid), classified into:
  - a. 22 pairs of homologous (similar) chromosomes called **autosomes**
  - b. One pair of **sex chromosomes**: XX in ♀ & XY in ♂
- o Each **gamete** (germ cells: ovum & sperm) contains 23 chromosomes ( $23 = n$  = haploid)
  - a. 22 autosomes
  - b. One sex chromosome: X in ova & X or Y in sperms
- o The **zygote** contains 46 chromosomes: 23 chromosomes from each parent

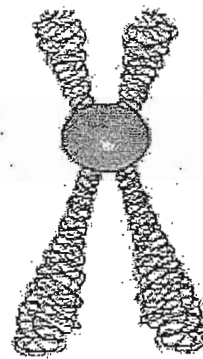
## Structure of Chromosomes

- During cell division, each chromosome is formed of 2 chromatids connected together at the centromere. The centromere divides the chromosome into:
  - a. Short arm = p arm (**p** for **p**etit)
  - b. Long arm = q arm
- Chromosomes can be classified according to position of the centromere into:
  - Metacentric: Centromere is very near to the center
  - Submetacentric: Centromere midway between the center & end
  - Acrocentric: Centromere is very near to the end
- Chromosomal ends are called **telomeres**

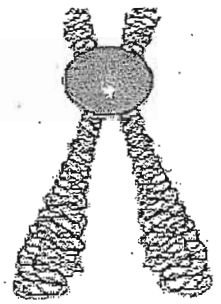
NB: Anti-centromere Ab in scleroderma



Metacentric



Submetacentric



Acrocentric

## Gene

- It is a DNA sequence that directs the synthesis of a specific polypeptide chain
- Number of human genes is about 25,000 genes

## Locus

It is the **site** of a gene on a chromosome

## Allele

- It is alternative form of a gene found at the same locus on a chromosome. Alleles on homologous chromosomes may be:
- Each trait is controlled by 2 alleles (One from each parent), which may be:
  - a. **Homozygous**: Identical (they may be normal or not)
  - b. **Heterozygous**: Different
  - c. **Hemizygous**: there is only one set for genes on X or Y chromosomes in **males**

## Homologous chromosomes

- They are chromosomes which pair during meiosis & contain identical loci
- X & Y chromosomes are not homologous (Different in size & shape)

## Dominant gene

It expresses itself whether homozygous or heterozygous

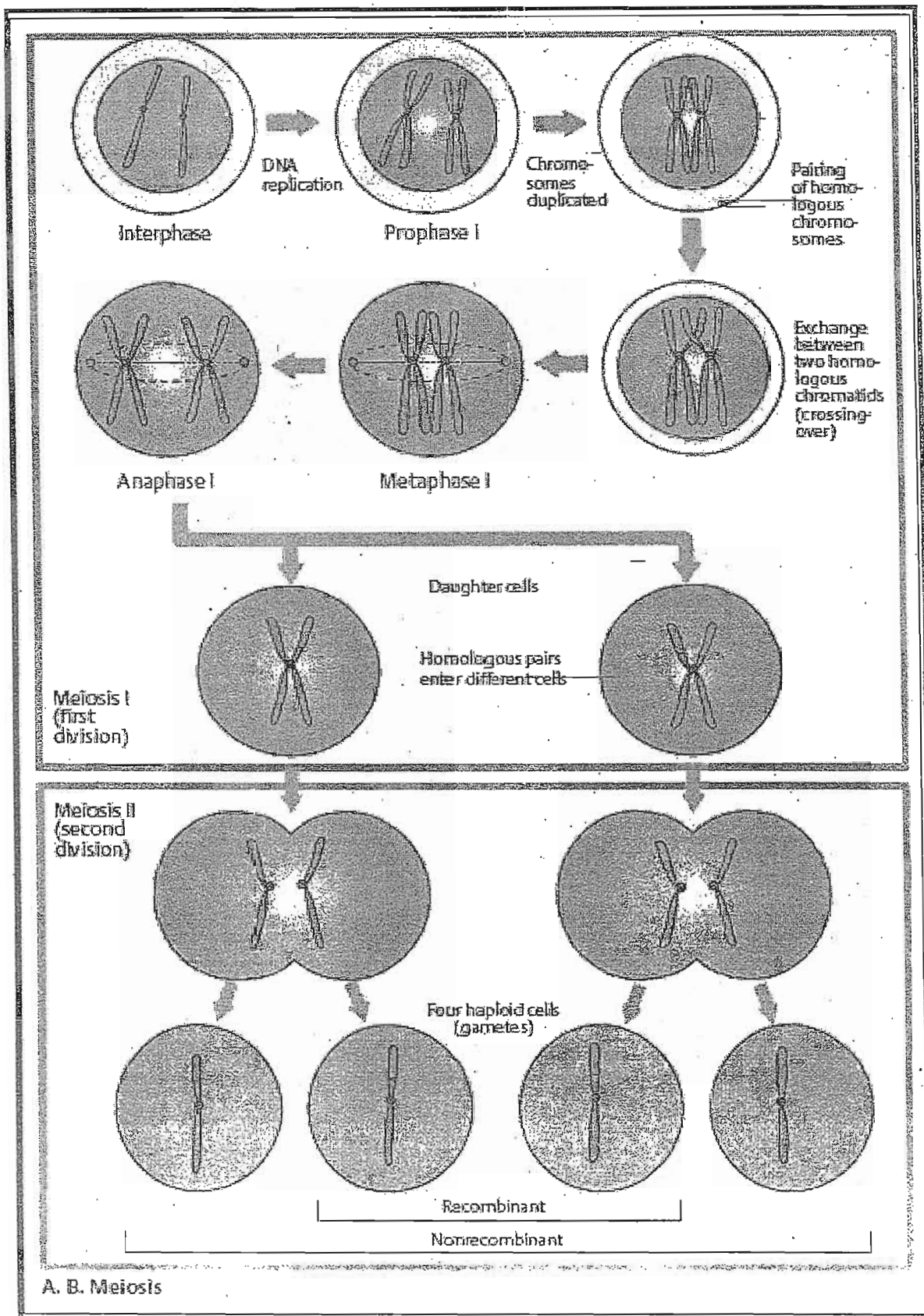
## Recessive gene

It expresses itself only if homozygous

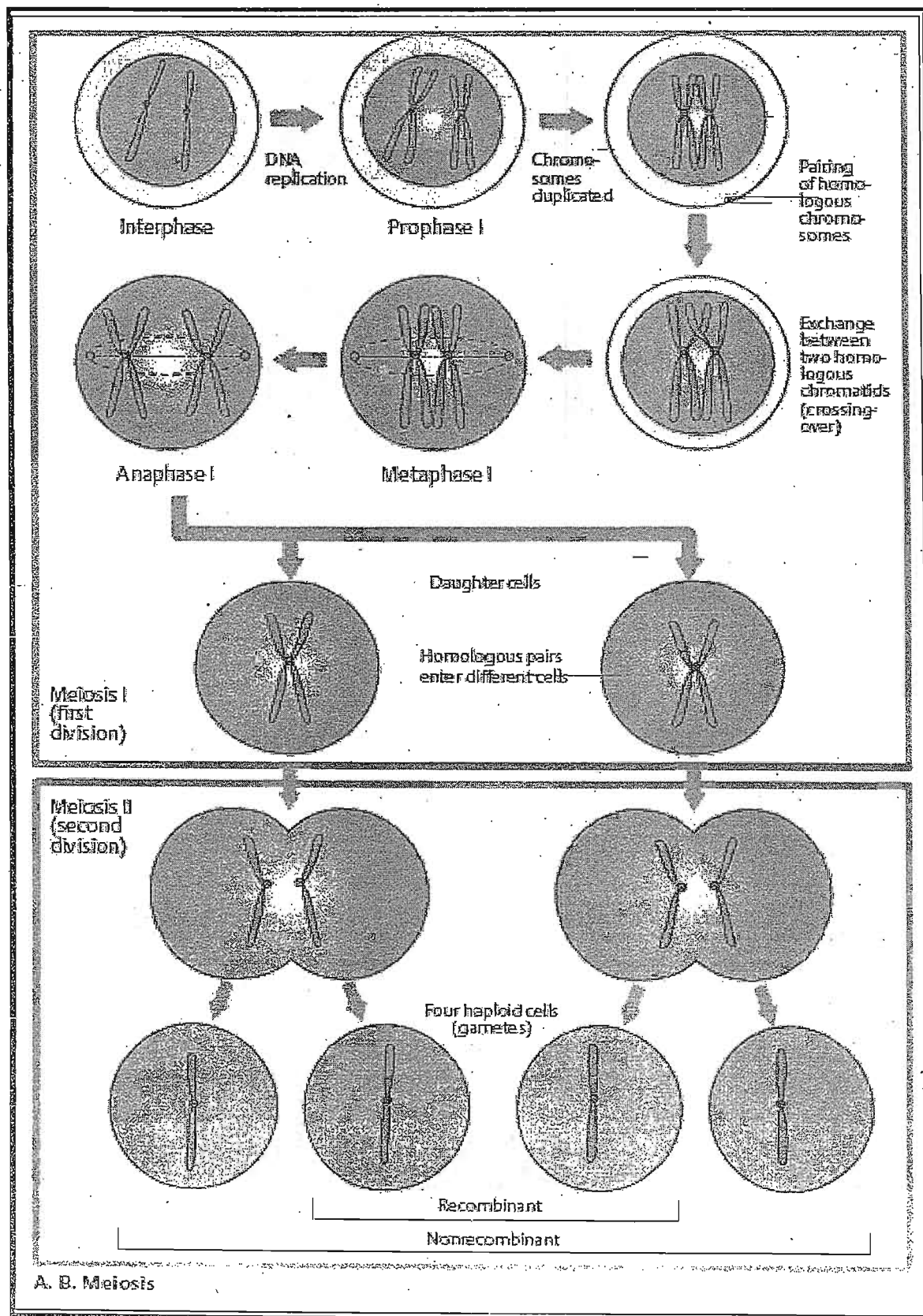
## Codominant genes

Both genes are expressed in the heterozygous

# Meiosis



# Meiosis





# Cell Cycle

## Definition

- It is the time taken by the cell to divide into 2 daughter cells.
- It is divided into interphase (3 stages) & mitosis:

	Stage	Duration	Events
Interphase	G <sub>1</sub> (gap 1)	9 hours	Formation of enzymes & nucleotides
	S (synthesis)	9 hours	DNA synthesis (gene duplication)
	G <sub>2</sub> (gap 2)	4 hours	Preparation for mitosis
	Mitosis	1-2 hours	Cell division

G<sub>0</sub> (gap 0) is the stage of quiescent cells which may be transient or permanent (nerve cells)

## Cell Division

There are 2 types of cell division:

- Mitosis: occurs in somatic cells → 2 daughter cells (2n) "Diploid number"
- Meiosis: occurs in germ cells → 4 daughter cells (n) "Haploid number"
  - ☒ First meiotic division: Reduction division
  - ☒ Second meiotic division: as mitosis

Mitosis	Meiosis (1 <sup>st</sup> meiotic division)
Preceded by Interphase	
<b>A) Prophase:</b> <ul style="list-style-type: none"> <li>Nucleus: swell</li> <li>Nuclear membrane: disappears</li> <li>Chromatin: <b>condensation</b> into chromosomes</li> <li>Chromosomes: visible; formed of 2 chromatids</li> <li>Centrioles: migrate to the opposite poles</li> <li>Spindle: formed &amp; attached to chromosomes</li> </ul>	<b>A) Prophase I:</b> <ul style="list-style-type: none"> <li><b>Leptotene (thread):</b> chromosomes are thread-like</li> <li><b>Zygotene (pairs):</b> chromosomes are paired</li> <li><b>Pachytene (thick):</b> chromosomes are formed of chromatids + <b>crossing over</b> (2 chromatids)</li> <li><b>Diplotene (double):</b> tetrad + chiasmata</li> <li><b>Diakinesis (motion):</b> homologous chromosomes start to move apart</li> </ul>
<b>B) Metaphase</b> Chromosomes are <b>arranged</b> in the equatorial plane ( <i>Homologous chromosomes do not react</i> )	<b>B) Metaphase I</b> Homologous chromosomes are arranged in the equatorial plane
<b>C) Anaphase</b> <ul style="list-style-type: none"> <li><b>Contraction</b> of the spindle</li> <li>Separation of sister chromatids at the centromere</li> <li>Each chromatid is now called chromosome</li> </ul>	<b>C) Anaphase I</b> <ul style="list-style-type: none"> <li>Contraction of the spindle</li> <li>Separation of homologous chromosomes</li> </ul>
<b>D) Telophase</b> <ul style="list-style-type: none"> <li><b>Cleavage</b> of the cytoplasm &amp; cell membrane</li> <li>Decondensation of chromosomes → chromatin</li> <li>2 daughter cells (2n) are formed "diploid"</li> </ul>	<b>D) Telophase I</b> <ul style="list-style-type: none"> <li>Cleavage of the cytoplasm &amp; cell membrane</li> <li>Decondensation of chromosomes → chromatin</li> <li>2 daughter cells (n) are formed "haploid"</li> </ul>
Meiosis (2 <sup>nd</sup> meiotic division) = As mitosis (pro- meta- ana- & telophase)	

### Crossing over (recombination):

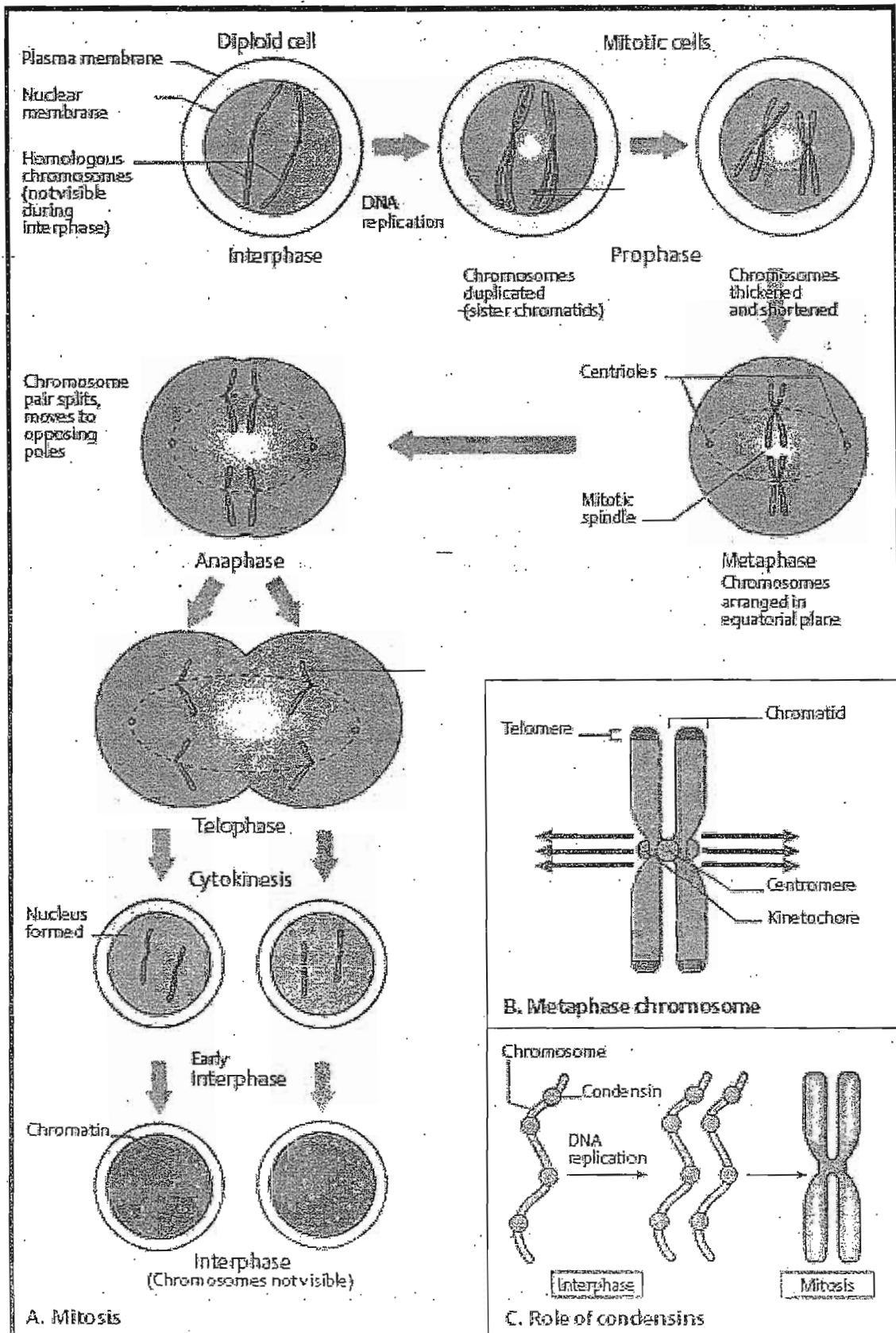
**Definition:** Physiologic process occurring during **meiosis** (Pachy- & Diplotene) at the area of **chiasmata**

**Process:** Breakage & exchange of genetic material between chromatids of *homologous* chromosomes

**Value:** Genetic recombination (variation)

Crossing over between 2 **sister** chromatids occurs in Bloom syndrome (↑↑ Risk of malignancy)

# Mitosis

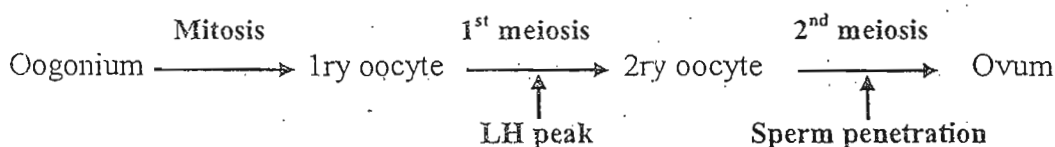


# Gametogenesis

## Definition

It is the production of gametes (sperm or ovum); by spermatogenesis or oogenesis

	Spermatogenesis	Oogenesis
Site	Seminiferous tubules	Ovary
Onset	At puberty	Fetal life
Course	Continuous	Interrupted at Prophase I & Metaphase II
Mitosis	Spermatogonia → 1ry spermatocyte	Oogonia → 1ry oocyte
1 <sup>st</sup> meiotic division	2 secondary spermatocytes	One 2ry oocyte + 1 polar body
2 <sup>nd</sup> meiotic division	4 sperms	One ovum + 3 polar bodies
Telophase I, II	Equal division of the cytoplasm	Unequal division of the cytoplasm



## Karyotyping

### Definition

It is the number, size & shape of the chromosomes in the cell

### Methodology of Karyotyping

Chromosomes are best seen during metaphase

#### 1. Type of the cells:

- ☒ To study mitosis: lymphocytes, skin fibroblasts, amniocytes, chorionic villi cells
- ☒ To study meiosis: Gonadal biopsy

#### 2. Culture of the cells on suitable medium (to ↑↑ number)

#### 3. Stimulation of cell division by adding mitogenic agent [Phytohemagglutinin (PHA)]

#### 4. Incubation for 72 hrs

#### 5. Inhibition of cell division at metaphase by colchicine (It inhibits spindle formation)

#### 6. Addition of hypotonic solution → Cell swelling & rupture

As in osmotic fragility test

#### 7. Separation & staining of chromosomes

- ☒ G banding: Staining with Giemsa stain → alternating dark & light bands
- ☒ Q fluorescence using quinacrine

#### 8. Chromosomes are photographed, cut & arranged in pairs in a standard manner

### Number

See before

### Structure

### Classification of chromosomes

#### A) According to the shape (position of the centromere):

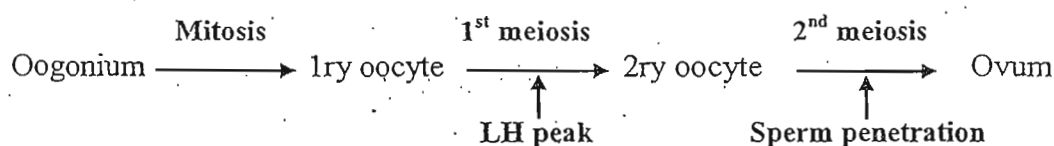
1. Metacentric: Centromere is very near to the center
2. Submetacentric: Centromere midway between the center & end
3. Acrocentric: Centromere is very near to the end
4. Satellite: a small part of chromatin is attached by a narrow stalk to the short arm of acrocentric chromosome

## Gametogenesis

### Definition

It is the production of gametes (sperm or ovum); by spermatogenesis or oögenesis

	Spermatogenesis	Oögenesis
Site	Seminiferous tubules	Ovary
Onset	At puberty	Fetal life
Course	Continuous	Interrupted at Prophase I & Metaphase II
Mitosis	Spermatogonia → 1ry spermatocyte	Oogonia → 1ry oocyte
1 <sup>st</sup> meiotic division	2 secondary spermatocytes	One 2ry oocyte + 1 polar body
2 <sup>nd</sup> meiotic division	4 sperms	One ovum + 3 polar bodies
Telophase I, II	Equal division of the cytoplasm	Unequal division of the cytoplasm



## Karyotyping

### Definition

It is the number, size & shape of the chromosomes in the cell

### Methodology of Karyotyping

Chromosomes are best seen during metaphase

#### 1. Type of the cells:

- ☒ To study mitosis: lymphocytes, skin fibroblasts, amniocytes, chorionic villi cells
- ☒ To study meiosis: Gonadal biopsy

#### 2. Culture of the cells on suitable medium (to ↑↑ number)

#### 3. Stimulation of cell division by adding mitogenic agent [Phytohemagglutinin (PHA)]

#### 4. Incubation for 72 hrs

#### 5. Inhibition of cell division at metaphase by colchicine (It inhibits spindle formation)

#### 6. Addition of hypotonic solution → Cell swelling & rupture

As in osmotic fragility test

#### 7. Separation & staining of chromosomes

- ☒ G banding: Staining with Giemsa stain → alternating dark & light bands
- ☒ Q fluorescence using quinacrine

#### 8. Chromosomes are photographed, cut & arranged in pairs in a standard manner

### Number

### Structure

See before

### Classification of chromosomes

#### A) According to the shape (position of the centromere):

1. Metacentric: Centromere is very near to the center
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3. Acrocentric: Centromere is very near to the end
4. Satellite: a small part of chromatin is attached by a narrow stalk to the short arm of acrocentric chromosome

## B) According to the size:

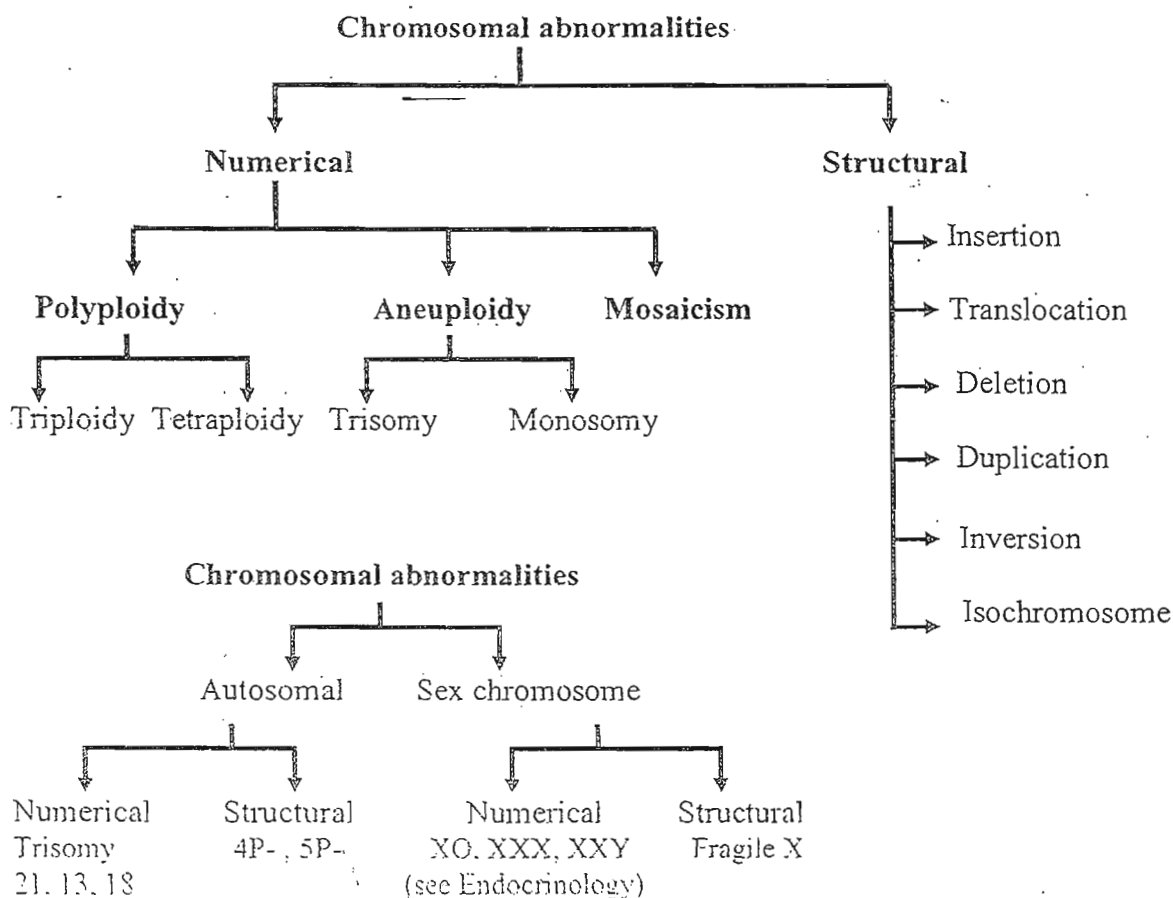
- ☒ Group A: 1-3
- ☒ Group B: 4,5
- ☒ Group C: 6-12 & X
- ☒ Group D: 13-15

- ☒ Group E: 16-18
- ☒ Group F: 19,20
- ☒ Group G: 21,22 & Y.

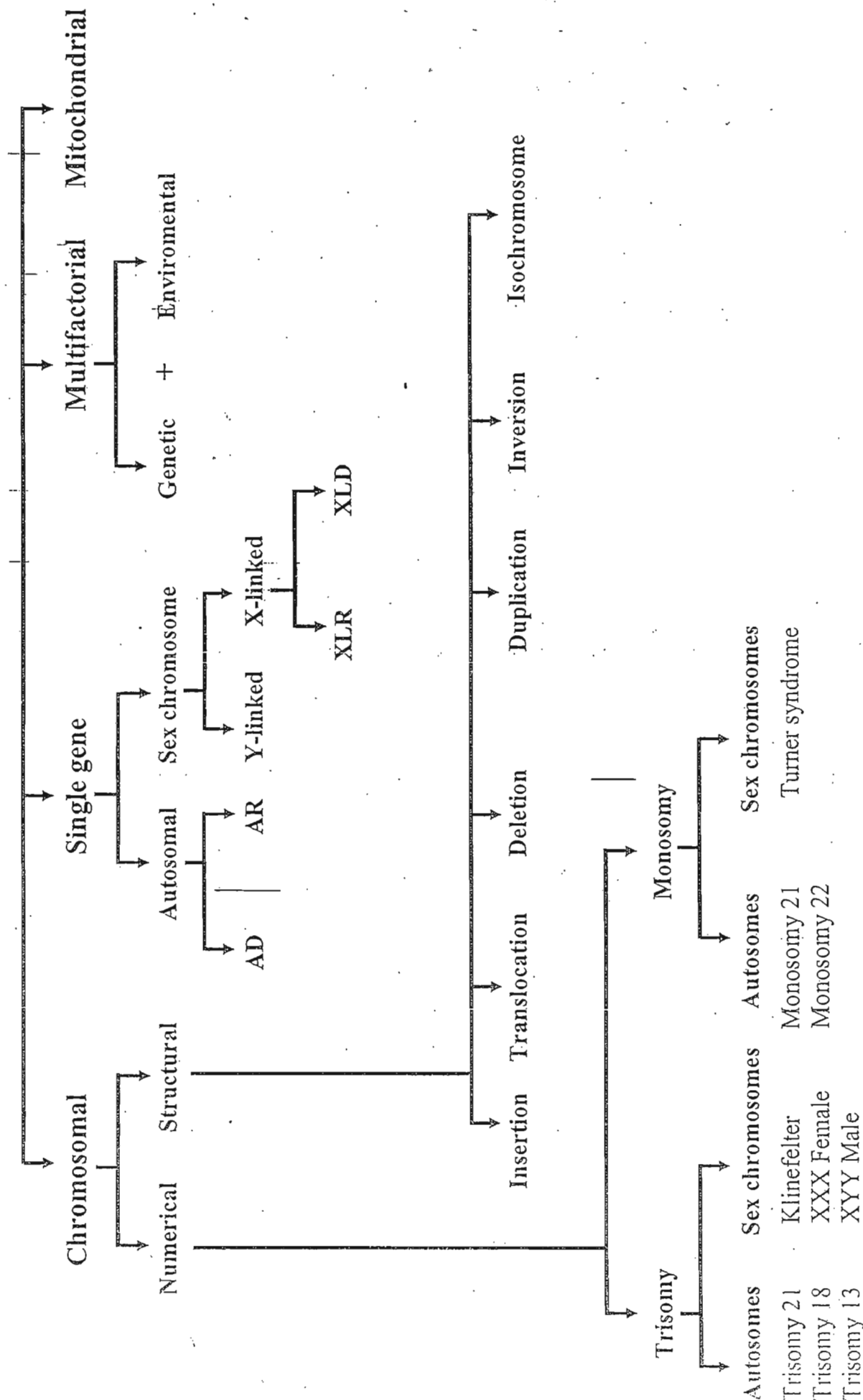
The largest is 1  
The smallest is 21??

## Indications of Karyotyping

1. Spontaneous abortion (7.5% of abortions have chromosomal abnormalities)
2. Congenital malformation & dysmorphology
3. Developmental delay & mental retardation
4. Atypical (ambiguous) genitalia
5. Disorders of sex development (complete androgen insensitivity...)
6. Short stature (♀)
7. Primary amenorrhea
8. Infertility
9. Antenatal (done on amniocytes or chorionic villous sample):
  - ☒ Old maternal age > 35 years
  - ☒ +Ve family history of chromosomal anomalies
  - ☒ +Ve maternal serum screening test for trisomy 21
  - ☒ +Ve US screening test for trisomy 21
  - ☒ Fetal sex determination in X-linked diseases
10. Malignancy
  - ☒ Retinoblastoma: mutation of chromosome 13 (RB1 gene)
  - ☒ Wilms tumor: mutation of chromosome 11 (WT1 gene)
  - ☒ Chronic myeloid leukemia: Philadelphia chromosome (translocation of a segment of 22 to 9)



# Genetic Disorders



# Chromosomal abnormalities

## Definition

Abnormalities in the number or the structure of the chromosomes

## Classification

### A) Numerical aberrations:

#### 1. Polyploidy:

Any multiple of the haploid number of chromosomes (*except normal diploid*)

a. Triploidy [ $3n = 3 \times 23 = 69$  chromosomes]

Causes:

- ☒ Failure of spindle formation during 1<sup>st</sup> *meiotic* division (in gametogenesis)
- ☒ Fertilization of 1 ovum with 2 sperms

b. Tetraploidy [ $4n = 4 \times 23 = 92$  chromosomes]

Causes:

- ☒ Failure of telophase of the 1<sup>st</sup> *mitotic* division of the zygote

#### 2. Aneuploidy

Abnormal number of a particular chromosome (*normally each chromosome has 2 copies*)

##### a. Trisomy

Definition: One chromosome is represented by 3 copies not 2 "extra chromosome"

Examples: Trisomy 21, 18, 13

##### b. Monosomy

Definition: One chromosome is represented by one copy not 2 "absent chromosome"

Examples: Turner syndrome (XO)

Causes of aneuploidy:

- ☒ Non-disjunction during meiosis:
  - Anaphase I: (non-disjunction of homologous chromosomes)
  - Anaphase II: (non-disjunction of sister chromatids)
- ☒ Anaphase lag: (Delayed movement of a chromosome during anaphase)

**Causes of non-disjunction:**

- ☒ Old maternal age ( $\uparrow\uparrow$  Teratogen exposure, weak chiasmata)
- ☒ Ionizing & non ionizing radiation
- ☒ Chemicals e.g., alkylating agents
- ☒ Familial tendency

#### 3. Mosaicism & chimerism

**Mosaicism:** the presence of 2 or more different cell lines derived from 1 fertilized ovum

It is post-fertilization event

**Chimerism:** the presence of 2 or more different cell lines derived from  $>1$  fertilized ovum

Examples: twins (TTTS), bone marrow transplantation, recombinant DNA

### B) Structural aberrations:

**Etiology:**

- ☒ Ionizing & non-ionizing radiation
- ☒ Chemicals e.g., alkylating agents
- ☒ Inherited diseases
- ☒ Spontaneous

**Inherited causes of chromosomal breakage:**

1. Fanconi anemia
2. Ataxia telangiectasia
3. Bloom syndrome
4. Xeroderma pigmentosa

Some changes occur in the genome through natural processes e.g., crossing-over during meiosis

### 1. Insertion "ins"

One piece of chromosome breaks at 2 points & is incorporated into a break in the same or other chromosome (3 breaks are needed)

### 2. Translocation

#### a. Reciprocal translocation "t"

Exchange of genetic material between non-homologous chromosomes

Usually it does not cause any abnormality (except if disruption of a normal gene occurs)

#### b. Robertsonian translocation "rob"

- Deletion of the short arms of 2 acrocentric chromosomes & centromere of one of them
- The long arm & centromere of one chromosome is translocated to the long arm of the other
- So, the total number of chromosome is 45 (numerical aberration)
- But with *normal* phenotype [Balanced translocation carrier]

### 3. Deletion "del"

Loss of part of chromosome

#### a. Terminal

Loss of one end of the chromosome (one break)

#### b. Interstitial

Loss of part between 2 fragments of the chromosome (2 breaks)

#### c. Ring

Loss of both ends of the chromosome (2 breaks), with folding "ring formation"

Deletion may be detected by routine chromosomal preparations (5p = Cri-du-chat)

**Microdeletions** can be detected by cytogenetic studies (FISH)

## Microdeletion Syndromes

Syndrome	Chromosome
1. Prader-Willi	15
2. Angelman	15
3. Williams	7
4. WAGR	11
5. Alagille	20
6. DiGeorge	22

### 4. Duplication "dup"

The presence of 2 copies of a segment of a chromosome

It results from unequal crossing-over during meiosis

Example: Charcot-Marie-Tooth disease (HMSN-I)

### 5. Inversion "inv"

End-to-end reversal of a segment within a chromosome (2 breaks are needed)

- Pericentric: around the centromere (both arms)
- Paracentric: involving one arm

### 6. Isochromosome "iso"

Transverse division of a chromosome at the centromere during meiosis followed by duplication → One chromosome with 2 long arms

One chromosome with 2 short arms



# Down syndrome

(Trisomy 21)

## Definition

It is numerical chromosomal abnormality (Trisomy 21) in which the cell contains 3 copies of chromosome number 21 instead of 2 (i.e., Extra chromosome 21).

**Incidence** 1: 700

## Genetic Types

- ☒ Non-disjunction (95%): Usually during maternal meiosis [Resulting in ovum with 24 chromosomes (Two chromosome 21 instead of one)]
- ☒ Translocation (4%): The extra-21 chromosome is translocated to another acrocentric chromosome (group D 13-15 or group G 21-22)  
One of the parents should be translocation carrier [= **Balanced translocation carrier**]
- ☒ Mosaicism (1%): Post-fertilization event [= Non-disjunction during zygote mitosis]

## Number of chromosomes & Recurrence risk

Type	%	Mechanism	No of chromosome	Maternal age	IQ	Recurrence risk
Non-disjunction	95 %	Non-disjunction 'Maternal meiosis'	47	Age dependent	Low	
Translocation	4 %	Translocation	46 (The extra chromosome is translocated to another one)	Non-age dependent	Low	
Mosaicism	1 %	Post-fertilization event	46/47	± Age dependent	Better	??

## Recurrence risk of Down syndrome

### A) Non-disjunction:

- Depends on the maternal age
- Risk is increased with advanced maternal age
- Examples:
  - At the age 20 yr = 1/2000
  - At the age 30 yr = 1/1000
  - At the age 40 yr = 1/100
  - At the age 50 yr = 1/10

### B) Translocation: Depend on the chromosome to which the "extra-21" is translocated

#### a. Translocation to D-group

- 1/3 Down
- 1/3 normal
- 1/3 translocation carrier

#### b. Translocation to chromosome 21

- 100 % Down

### C) Mosaicism

- Minimal

## Clinical Picture

- A) **Delayed mental development (MR):** Social smile, recognition of mother, speech ...  
B) **Delayed motor development (hypotonia):** Head support, sitting, crawling, walking...  
C) **Characteristic dysmorphic features:**

☒ **Skull**

Brachycephaly, delayed closure of AF, microcephaly

☒ **Hair**

Silky

☒ **Eye**

Upward slanting palpebral fissure

Medial epicanthal folds

Speckled iris (brushfield iris)

Cataract (3 %), squint

☒ **Nose**

Depressed nasal bridge

☒ **Ears**

Malformed, overfolded helix

Underdeveloped ear lobule

☒ **Mouth**

Small oral cavity

Protruded & fissured Tongue

☒ **Neck**

Short & broad

Atlantoaxial instability

☒ **Hands**

Short & broad hands

Clinodactyly (Incurved little finger)

Simian crease (Single transverse palmar crease)

☒ **Feet**

Short & broad feet

Wide gap between 1<sup>st</sup> & 2<sup>nd</sup> toes (Sandal gap 97%)

☒ **Abdomen**

Distension, hernia

☒ **Chest**

Recurrent chest infections, why? →

☒ **Neurological**

Hypotonia

Alzheimer disease in the majority by the age of 40 yrs



### **Remember**

- **Down:** Small oral cavity
- **Cretinism:** Large tongue

50% of Down \$ have simian crease  
4% of population have simian crease

### **Causes of chest infection:**

1. CHD
2. Hypotonia
3. Leukemia (↓↓ Immunity)

D) **Associated congenital anomalies:**

- a. **Cardiac (40%):** Endocardial cushion defects (AV canal), VSD, ASD, PDA or Fallot
- b. **GIT (6%):** Duodenal atresia, annular pancreas, imperforate anus
- c. **Renal anomalies**

E) **Complications:**

- a. Cardiac complications (Heart failure)
- b. Recurrent chest infection
- c. Increased risk of leukemia (AML, ALL) 10-20 folds more than the general population
- d. Normal survival is expected in absence of complications (CHD)
- e. ↑↑ Risk of DM, obesity, thyroiditis & epilepsy

## Investigations

### A) Cytogenetic studies

- Karyotyping is essential in every patient to determine the type & recurrence risk
- In translocation Down, karyotyping of the parents and other relatives is required
- FISH

### B) Imaging

- CXR, ECG, Echocardiography (CHD)
- Abdominal X-rays (Imperforate anus)
- Abdominal US (GIT & Renal anomalies)

## Antenatal Diagnosis

### Indications:

- ☒ Old maternal age > 35 years
- ☒ Previous baby with Down syndrome
- ☒ Family history of Down syndrome
- ☒ Family history of translocation

### Methods:

1. Triple test: done in maternal serum at 15-16 weeks of gestation
  - ↓↓ α-Fetoprotein
  - ↓↓ Unconjugated estriol
  - ↑↑ β-hCG (Human chorionic gonadotropin)
2. Dimeric inhibin; marker in maternal serum (↑↑ in Down syndrome)
3. Fetal karyotyping:
  - Amniocentesis: 14-16 weeks of gestation
  - Chorionic villus sample: 9-12 weeks of gestation
  - Fetal cells in maternal circulation
4. Fetal US
  - Nuchal Translucency thickening: thickening of the nuchal fold at the back of the neck due to delayed drainage of fluid from the upper part of the body
  - Short femur
  - Cystic hygroma of the neck, duodenal stenosis

## Treatment

No specific Rx-Supportive

Rehabilitation

Surgical correction of congenital anomalies

Do not say "a Down baby" but  
"a baby with Down syndrome"

## Common Autosomal Trisomies

	Trisomy 18 (Edwards S)	Trisomy 13 (Patau S)
<b>Incidence</b>	1/4000	1/6000
<b>Genetic type</b>	Non-disjunction	Non-disjunction
<b>Features</b>	Prominent occiput (Dolicho-) Microcephaly Eye anomalies Small ears Cardiac (VSD, PDA) Overlapping fingers (closed fist) Rocker-bottom (protruding calcaneus)	Microphthalmia Microcephaly Cleft lip Cleft-palate Cardiac (VSD, PDA) Omphalocele Rocker-bottom (protruding calcaneus)
<b>Survival</b>	> 90% die in infancy	> 90% die in infancy



**Trisomy 18**  
(Overlapping fingers)



**Trisomy 13**  
(Microcephaly, cleft lip & palate)

## Autosomal deletion syndromes

### 4p-

- Prominent forehead
- Broad nasal root [Greek helmet face]
- Short filtrum
- CHD

### 5p- (Cri-du-chat syndrome)

- Microcephaly
- Round face
- Hypertelorism
- Low set ears
- Hypotonia
- Cat-like cry

# Sex Chromosome Abnormalities

- A) Turner syndrome (XO)      C) XXX female  
B) Klinefelter syndrome (XXY)      D) Fragile X syndrome

## Fragile X Syndrome

**Definition:** It is the second most common genetic cause of MR after Down syndrome

**Incidence:** 1/4000

**Mode of inheritance:** XL-R (FMR1 gene)

**Genetic Defect:** Fragile site in the distal part of the long arm of the X chromosome

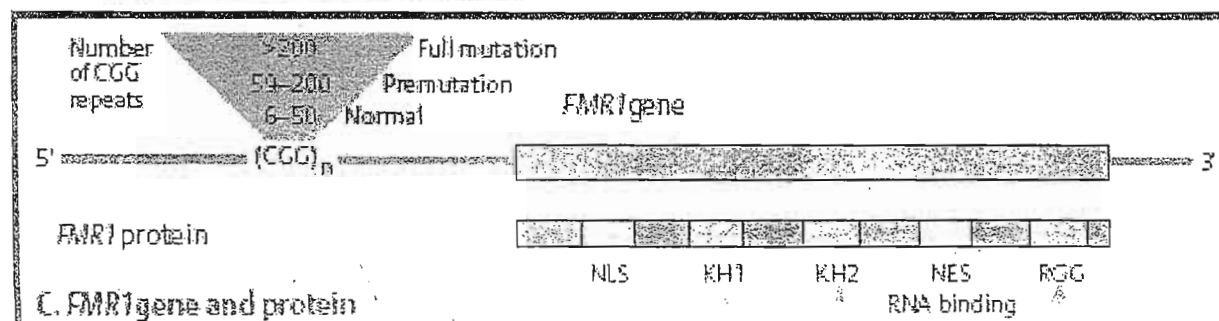
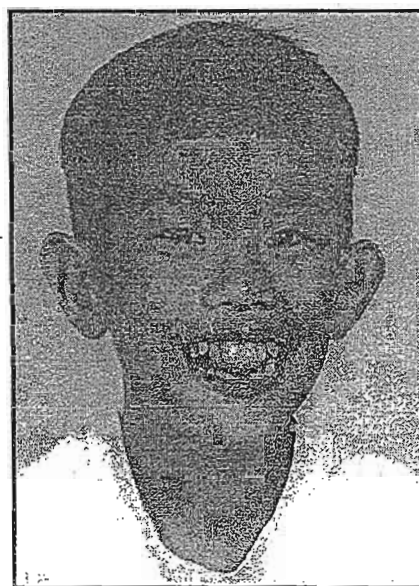
**Molecular analysis:** Tri-nucleotide repeat expansion [CGG] that may ↑↑ in size "expansion" through females in successive generations

**Clinical Picture:**

- a. ♂: Mental retardation  
Macro-orchidism (When?)  
Facies: Long face, large everted ears, broad forehead, prominent mandible  
Behavioral: Autistic & / or hyperactive behavior  
Cardiac: Mitral valve prolapsed
- b. ♀: Variable degrees of MR (usually mild to moderate) & learning disability

**Diagnosis:** Detection of CGG repeat number (PCR)

	Repeat	Normal	Premutation	Affected
Fragile X syndrome	CGG	< 50	55-199	> 200
Myotonic dystrophy	CTG	5-37	37-50	> 50
Huntington Chorea	CAG	5-37	-	> 40-55



# Turner Syndrome

## Genetic Types

- ☒ Non-disjunction (most common): The X chromosome is usually of maternal origin
- ☒ Mosaicism (better prognosis): 45, X / 46, XX

## Clinical picture

(A) **At birth:** Edema of dorsum of hands & feet

(B) **Childhood:**

- Short stature (Mean = 143 cm)
- Webbing of the neck
- Widely spaced nipples
- Cubitus valgus (↑↑-carrying angle)
- Low posterior hair line
- Normal mentality (MR in 18%)
- Cardiac: Coarctation, bicuspid aortic valve
- Renal: Horseshoe, ectopic kidney...
- Thyroiditis (30%): Hypothyroidism
- IGT, Type II DM

(C) **Puberty:**

- Secondary sex characters fail to develop

## Investigations

1. Estrogen level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. Karyotyping (45, X)
4. U/S, Echocardiography, Thyroid profile

## Treatment

- **hGH**
- **Estrogens:** To induce the development of 2ry sex characters. Start at 11-12 yrs (Why?)
- **Estrogen + Progesterone cyclic therapy:**
  - Estrogen D1- D23
  - Progesterone D10- D23
  - No Rx D23-D30 → Withdrawal bleeding
- **Ovum donation + IVF:** ?? Fertility

	Turner	Neonan
<b>Sex</b>	Only ♀	♀ & ♂
<b>Genetics</b>	Non-disjunction	AD
<b>Cardiac</b>	CoA / bicuspid aortic valve	PS
<b>Mentality</b>	MR in 18%	MR more common
<b>Sexual Development</b>	Hypogonadism	Delayed (2yrs)

## Klinefelter Syndrome

**Incidence** 1:600-1.000 liveborn ♂

**Genotype** 47, XXY  
Variants: XXXY, XXXXY (↑↑ Severity)

**Etiology** Non-disjunction

### Clinical picture

- Disproportionate tall stature:
  - Span > height,
  - Lower segment > Upper segment
- Small testes (Prader Orchidometer)
- Gynecomastia (30%)
- Infertility (Azoospermia)

**Complications** Breast cancer, mediastinal germ cell tumors

**Treatment** Testosterone replacement therapy



## Poly-Y male (47, XYY male)

- No Hypogonadism
- Aggressive antisocial behavior & violence

## Triple-X female (47, XXX female)

- No Hypogonadism
- learning & behavioral disorders
- Normal fertility but early menopause is common

### **Noonan Syndrome:**

- Etiology: AD<sup>12</sup> (variable expression)
- Features of Turner \$ + **Normal karyotyping** + affecting ♀ & ♂
- Short stature, neck webbing, cubitus valgus
- Cardiac: Cardiomyopathy, PS, branch pulmonary artery stenosis
- Facies: Hypertelorism, epicanthus, ptosis, micrognathia, antimongloid slant, ear anomalies
- Hypogonadism: Delayed puberty (2 yrs later)
  - ♂: Small testes, cryptorchidism
  - ♀: Premature ovarian failure
- Mental retardation: 25-30%
- Rx: hGH

## X-Chromosome Inactivation (Lyon Hypothesis)

### Sex chromatin (Barr body)

- It appears in individual with  $\geq 2$  X chromosomes
- No. of sex chromatin = No. of X - 1
- Size of sex chromatin changes with change of the size of X chromosome

Inactivation occurs through methylation of cytosine

### Lyon Hypothesis (after Mary Lyon = 1961)

1. Sex chromatin in ♀ is genetically inactive X chromosome
2. Inactivation starts in the intra-uterine life
3. Inactivation is **random** but **fixed** (either paternal or maternal X chromosome and all cells derived from that cell)
4. Females are **mosaic** for X-linked genes

### Benefits of Lyon Hypothesis

1. It explains why the gene product of the 2Xs in ♀ is equal to gene product of 1 X in ♂
2. It explains why in XLR diseases, homozygous ♀ is affected equal to hemizygous ♂
3. It explains why heterozygous ♀ "Carrier" for XLR gene may show clinical / biochemical findings:
  - ☒ Duchenne muscular dystrophy: ↑↑ CK
  - ☒ Hemophilia: ↑↑ PTT
  - ☒ Ocular albinism: Patchy pigmentation of the fundus
  - ☒ Retinitis pigmentosa: Abnormal retinal reflex
4. In XLR diseases, if male is affected; there are one of 2 possibilities:
  - ☒ Mother is carrier: So test the mother for clinical / biochemical findings (as above)
  - ☒ New mutation (Mother is free)

### Disadvantages of Lyon Hypothesis

It fails to explain why Turner ♀ with one X is *not* normal, so other theories emerge:

1. Both X chromosomes are active early in IU life to allow normal development of XX
2. Some genes essential for normal development escape inactivation
3. Inactivation starts early but it is gradual allowing normal development
4. Both XX are active but they function as one X chromosome of a male

## Gene structure & Function

### Gene

- It is a DNA sequence that directs the synthesis of a specific polypeptide chain
- Most of the DNA (> 95%) **does not code** proteins with no known function
- Non-coding sequence lie within (introns) & between genes
- 45% of DNA is formed of repeat sequences (unknown function) called satellites, which vary among individuals "**DNA finger printing**"
- People are genetically very similar (99.9% identical)
- The 0.1% difference is not negligible as it corresponds to 3 millions nucleotides

No. of human genes ~ 25,000

### Pseudogene

It is DNA sequence resembling normal gene but has minor changes preventing its transcription

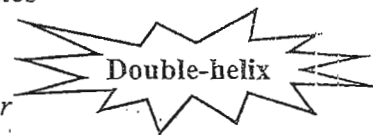
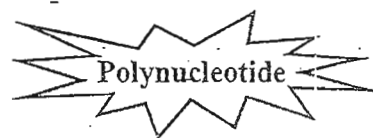
No. of nucleotides ~ 3 billions



## DNA

- It is a polynucleotide, double helix molecule formed of 2 complementary strands
- Nucleotide = Sugar + Phosphate + Nitrogenous base
- Sugar = Deoxyribose
- Nitrogenous bases
  - a. **Pyrimidines:** Thymine (T) & Cytosine (C)
  - b. **Purines:** Adenine (A) & Guanine (G)
- The outer backbone of the helix is formed of alternating sugars & phosphates
- The bases project inwards from the outer sugar-phosphate framework
- The bases are complementary:
  - A = T (2 hydrogen bonds)
  - G = C (3 hydrogen bonds)

*The bonds help to hold the 2 strands together & in the Repair of damaged DNA*
- The 2 strands run in opposite directions [one in 5'-3' & the other in 3'-5' direction]
- DNA is present in the nucleus (1% of total cellular DNA is present in the mitochondria)



## Functions of DNA

### A) Replication

- ☑ It occurs in the interphase before cell division
- ☑ Each strand acts as a template → synthesis of a new strand
- ☑ The new DNA molecule is formed of 2 strands; one *old* & one *new* [Semiconservative]
- ☑ Replication is catalyzed by **DNA polymerase**

### B) Transcription

- ☑ It is synthesis of mRNA molecule from a DNA template
- ☑ Only one strand acts as template [Template = Antisense]
- ☑ The other strand is called [Sense = Coding strand]??
- ☑ This is not fixed; a given strand may act as template for some genes & coding for others

The coding (Sense) strand has the same sequence of the synthesized RNA except.

### C) Translation

- ☑ It is protein synthesis via "translation" of genetic information carried on mRNA
- ☑ It occurs in the ribosomes (Cytoplasm)

## Mitochondrial DNA

- The mitochondrion contains 2-10 copies of double stranded DNA (mt-DNA)
- Size = 16 Kb (Kilobase)
- Circular
- No introns
- Exclusively transmitted by the mother [Sperm does not contain mitochondria]
- Slightly different genetic code (e.g., UGA codes for tryptophan not a stop codon)
- Mt-DNA codes for
  - 13 proteins (components of the respiratory chain)
  - 2 rRNA & 22 tRNA
- Mt-DNA mutations lead to mitochondrial diseases e.g., MELAS, MERRF, KSS

## RNA

	DNA	RNA
Name	Deoxyribonucleic acid	Ribonucleic acid
Site	Mainly in the nucleus (& mitochondria)	Mainly in the cytoplasm (& nucleus)
Sugar	Deoxyribose	Ribose
Bases	A, G, C, <u>T</u>	A, G, C, <u>U</u>
Strands	Two	One
Type	One	4 types (hnRNA, mRNA, tRNA, rRNA)
Shape	Double helix	Variable

## Organization of genes

- ☒ Exon: a segment of the gene that is represented in the final spliced mRNA
- ☒ Intron: a segment of the gene that is not represented in the final spliced mRNA because it has been removed during splicing of exons around it
- ☒ Boundaries between exons & introns are not random. Introns begin with GT & end with AG
- ☒ The gene is formed of Promoter, Transcription unit & Terminator
- ☒ RNA polymerase (RNAP) binds to the promoter
- ☒ The promoter contains:
  - a. **TATA boxes:** 25 nucleotides upstream (at the 5') the transcription unit.  
It allows **attachment & separation** of RNAP to the promoter
  - b. **CCAAT boxes:** 70 nucleotides upstream (at the 5') the transcription unit.  
It determines the **frequency** of transcription
- ☒ The promoter also contains:
  - a. **Enhancers:** ↑↑ Gene expression
  - b. **Silencers:** ↓↓ Gene expression

## Transcription

- ☒ It is synthesis of mRNA molecule from a DNA template (RNAP enzyme)
- ☒ Only one strand acts as template, the other strand is called the coding strand
- ☒ RNAP attaches to the promoter
- ☒ TATA box: Initiation of transcription
- ☒ CCAAT box: Frequency of transcription
- ☒ The primary transcript RNA undergoes the following modifications (Processing):
  1. Capping of 5' by GTP
  2. Methylation
  3. Addition of Poly-A tail
  4. Removal of introns & splicing of exons

4



## Translation

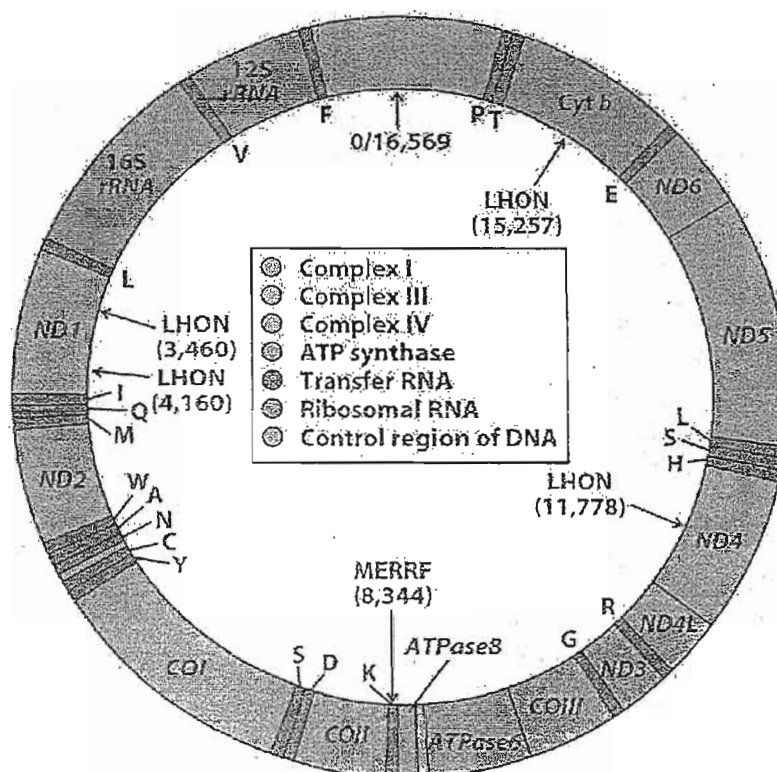
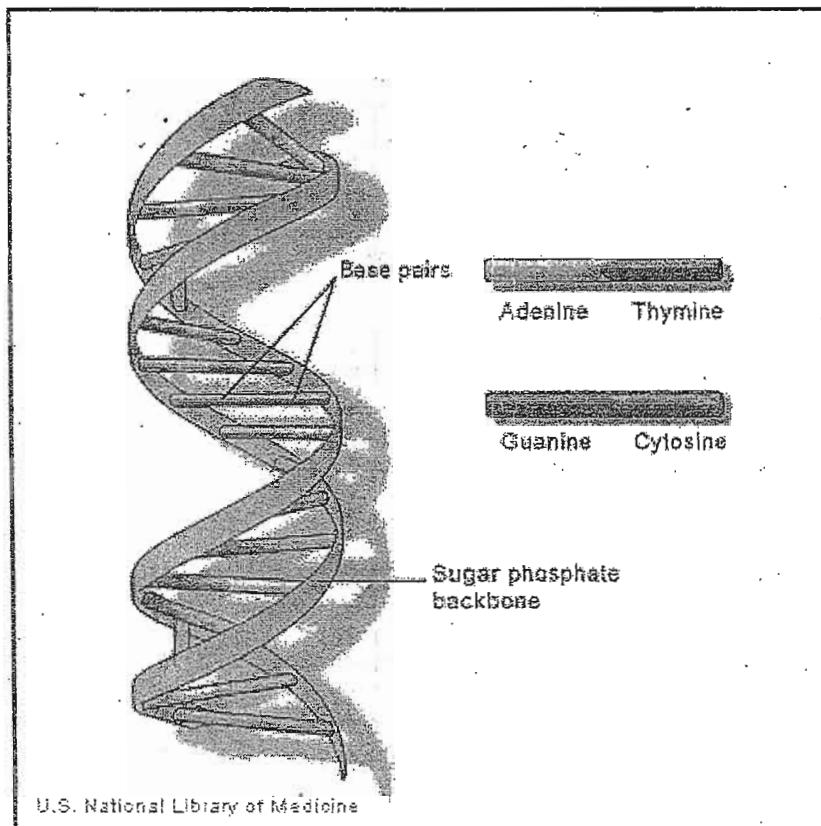
- ☒ It is protein synthesis via "translation" of genetic information carried on mRNA
- ☒ It occurs in the ribosomes (cytoplasm)
- ☒ The ribosome moves along mRNA in the 5'-3' direction, translating the successive codons
- ☒ The 1<sup>st</sup> codon to be translated is AUG (coding for methionine)
- ☒ tRNA brings the amino acids to mRNA-ribosome complex
- ☒ The anticodon on tRNA can recognize the complementary codon in the mRNA
- ☒ The process is repeated in 5'-3' direction till reaching a stop codon
- ☒ The polypeptide is released

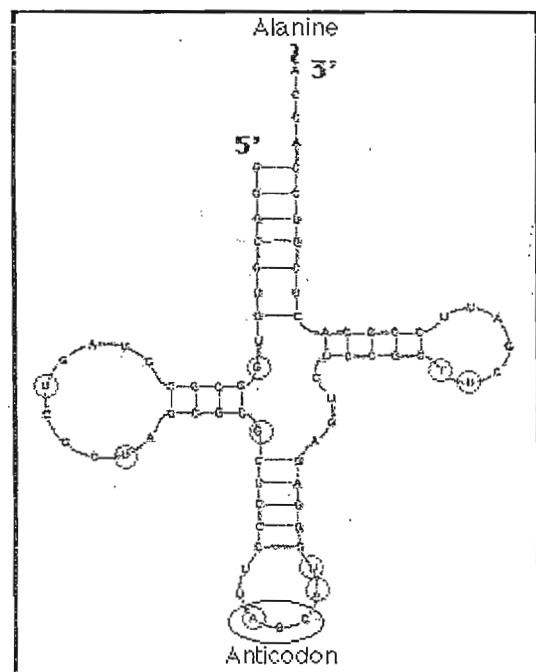
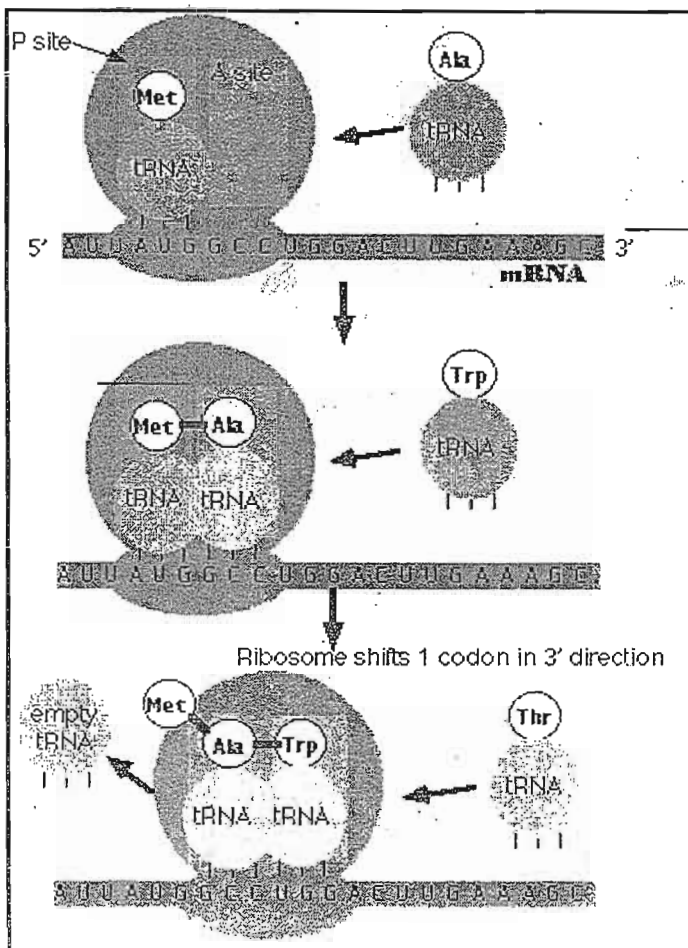
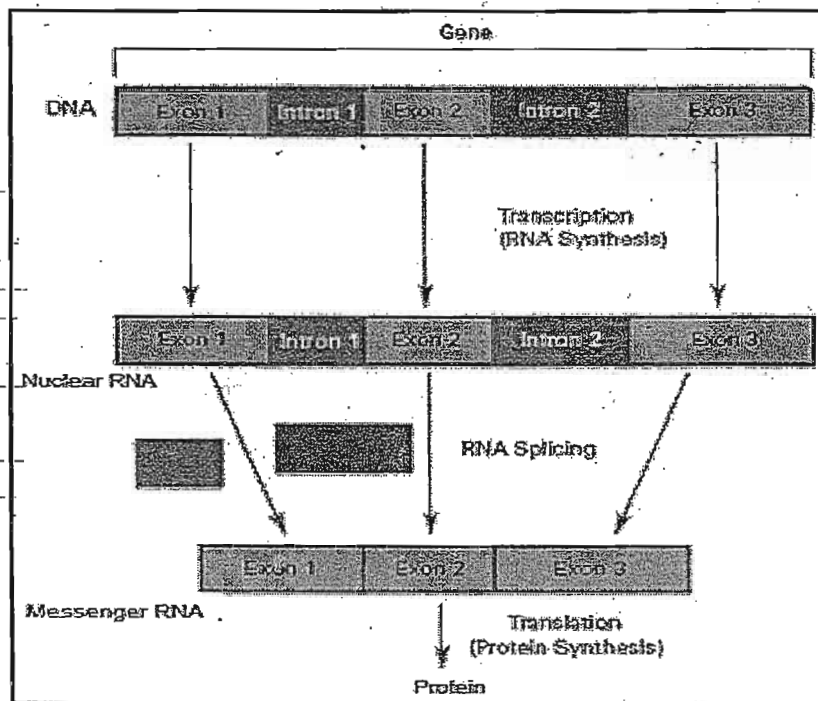
## Protein structure

- Primary: Polypeptide chains
- Secondary: Change in the configuration of the protein due to bonding between groups (e.g., hydrogen bonds lead to twisting into helix)
- Tertiary: 3-dimensional shape

## Control of gene expression (*All cells contain All genes necessary for every cell function*)

- ☒ TATA & CCAAT boxes
- ☒ Enhancers & Silencers [Either cis: near by the gene or trans: away from on other chromosome]
- ☒ Intronic sequence
- ☒ Methylation of genes (Methylation of the gene → ↓↓ Gene expression)
- ☒ Sequence 3' to the gene





## Genetic code (Codon)

### Definition

It is a sequence of 3 adjacent nucleotides in a nucleic acid that code for one amino acid

### Characteristics of the Codon

1. **Triplet** (3 adjacent nucleotides). We have 64 codons & 20 amino acids
2. Written in the **direction** 5'-3'
3. **Specific**: Certain codon always code for only one specific amino acid
4. **Universal**: applied to all organisms (Mitochondrial DNA has a slight different codons)
5. **Redundancy** (Degeneracy): a given amino acid may have more than one codon
6. **Initiating** codon = AUG (which codes for methionine)
7. **Stop** codons = UAG, UGA, UAA
8. The 3<sup>rd</sup> base of the codon is the least important e.g., Glycine has GGG, GGC, GGU, GGA
9. Amino acids with similar chemical properties have related codons (Codons with U in the middle are hydrophobic)
10. The mRNA codon is recognized by **complementary anti-codon** (a sequence of 3 adjacent nucleotides in the middle loop of tRNA molecule)

## Mutations

### Definition

Changes in the nucleotide sequence as a result of mutagen exposure (may be spontaneous)

### Classification

#### I) Point mutation (base substitution):

- ☒ Transition: Pyrimidine  $\longleftrightarrow$  Pyrimidine      or      Purine  $\longleftrightarrow$  Purine
- ☒ Transversion: Pyrimidine  $\longleftrightarrow$  Purine

#### Effects of point mutations:

1. **Silent** mutation: new codon but for the same amino acid (e.g., GGC  $\rightarrow$  GGA)
2. **Nonsense** mutation: if the resulting codon is a stop codon (e.g., AGA  $\rightarrow$  UGA)
3. **Sense** mutation: if a stop codon is changed into another coding one (e.g., UGA  $\rightarrow$  AGA)  
Hb constant spring ( $\alpha$  chain with 31 extra amino acids)
4. **Missense** mutation: different amino acid is formed. This change may be:
  - a. Acceptable: No change in protein function
  - b. Partially acceptable: Valine replaces glutamic acid in the  $\beta$ -chain of Hb resulting in the formation of HbS which still can carry  $O_2$
  - c. Unacceptable: HbM (Can not carry  $O_2$ )
  - d. Splicing mutation: Failure of splicing of exons

#### II) Addition or Deletion of nucleotides (Gene rearrangement):

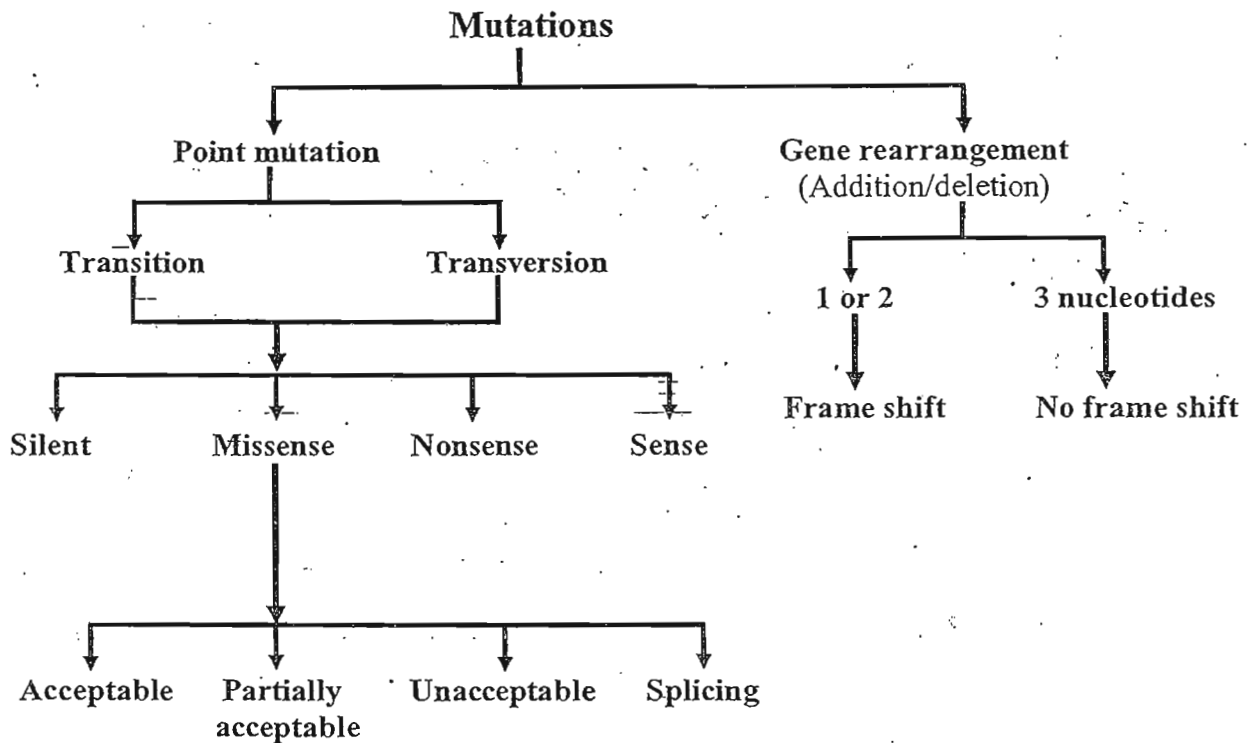
- ☒ One or two nucleotides: Frame shift (change of all codons on the 3' side)
- ☒ Three nucleotides: No frame shift (Addition or Deletion of one amino acid)

### Etiology (Mutagens)

- ☒ Ionizing & non-ionizing radiation
- ☒ Chemicals e.g., alkylating agents
- ☒ Inherited diseases??  $\Rightarrow$
- ☒ Spontaneous

### Types or mutation

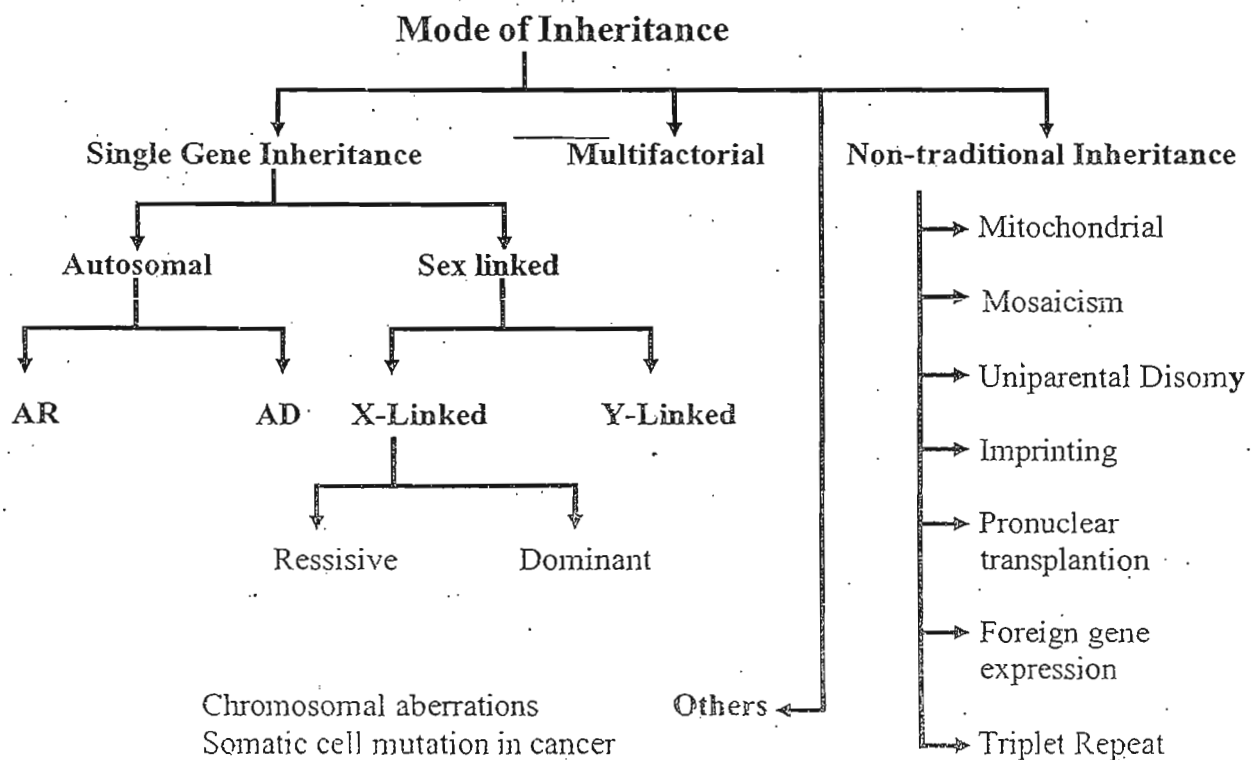
- ☒ Mutation of somatic cells: Non-heritable
- ☒ Mutation of germ cells: Heritable



### Classes of DNA

	Repeat size (bp)	Total size (kb)	Features
Satellite	5-200	~100	
Minisatellite	10-60	20	2 families; VNTR & telomeric family
Microsatellite	1-4	1	Repeats of A, CA

(VNTR = Variable number of tandem repeats)



# Mode of Inheritance

## **Mendel's Laws:**

1. Unit Inheritance
2. Segregation
3. Dominance
4. Independent assortment

## **A) Single Gene Inheritance**

### Gene

It is a DNA sequence that directs the synthesis of a specific polypeptide chain

### Locus

It is the site of a gene on a chromosome

### Allele

It is alternative form of a gene found at the same locus on a chromosome. Alleles on homologous chromosomes may be:

- a. Homozygous: identical (they may be normal or not)
- b. Heterozygous: different
- c. Hemizygous: there is only one allele for genes on X or Y chromosomes in males

### Dominant allele

It expresses itself whether homozygous or heterozygous

### Recessive allele

It expresses itself only if homozygous

**Codominance** = Both alleles are expressed in the heterozygous.

## Autosomal Inheritance

	Autosomal Dominant	Autosomal Recessive
<b>Affected Individual</b>	<ul style="list-style-type: none"> <li>May be homozygous or heterozygous</li> <li>One parent must be affected (except for new mutation)</li> </ul>	<ul style="list-style-type: none"> <li>Must be homozygous</li> <li>Both parents are heterozygous (carrier)</li> <li>Parental consanguinity → ↑↑ incidence</li> </ul>
<b>Sex</b>	♀ & ♂ are equally affected	♀ & ♂ are equally affected
<b>Carrier</b>	No carrier state	Carrier (phenotypically normal)
<b>Transmission</b>	Vertical (No skipping)	Transverse (skipping)
<b>Offsprings</b>	<ul style="list-style-type: none"> <li>Homozygous parent → 100% affected</li> <li>Heterozygous parent → 50% affected</li> <li>Heterozygous parents → 75% affected</li> </ul>	<ul style="list-style-type: none"> <li>Homozygous parent → 100% carrier</li> <li>Heterozygous parents → 25% affected, 25% normal, 50% carrier</li> </ul>
<b>Defect</b>	Structural	Functional
<b>Severity</b>	Usually less severe	Usually more severe
<b>Examples</b>	Huntington chorea, Myotonic dystrophy, Neurofibromatosis, Tuber sclerosis, Facioscapulohumeral muscular dystrophy, Osteogenesis imperfecta, Achondroplasia, Marfan, Ehler-Danlos, ADPKD, H.spherocytosis	Gaucher, Galactosemia, phenylketonuria, Homocystinuria, Hurler, albinism, SMA, CAH, Cystic fibrosis, Wilson, Cystinosis, GM <sub>1</sub> , GM <sub>2</sub> (Tay-Sachs, Sandhoff), Zellweger
<b>Pedigree</b>	<p style="text-align: center;">Aa   X   aa</p> <p style="text-align: center;"> <span style="margin-right: 40px;">Aa   Aa</span> <span>aa   aa</span> </p> <p style="text-align: center;"> <span style="margin-right: 40px;">50%</span> <span>50%</span> </p> <p style="text-align: center;"> <span style="margin-right: 40px;">Affected</span> <span>Normal</span> </p>	<p style="text-align: center;">Aa   X   Aa</p> <p style="text-align: center;"> <span style="margin-right: 40px;">AA   Aa   Aa</span> <span>aa</span> </p> <p style="text-align: center;"> <span style="margin-right: 40px;">25%</span> <span style="margin-right: 40px;">50%</span> <span>25%</span> </p> <p style="text-align: center;"> <span style="margin-right: 40px;">Normal</span> <span style="margin-right: 40px;">Carrier</span> <span>Affected</span> </p>

## Sex Linked Inheritance

### **A) Y-Linked Genes (Holandric Inheritance):**

- The trait is transmitted only in ♂ (♂ to ♂ transmission)
- Affected male has all his sons affected
- Examples: Hairy pinna

## B) X-Linked Genes:

### 1. X-linked Dominant:

- The same as AD transmission but:
- Affected ♂ transmits the trait to all of his daughters but **none** of his sons
- May be lethal in ♂

### 2. X-linked Recessive:

- Affected ♂ is hemizygous
- ♀ are affected (Homozygous) in the following conditions: →

**Affected ♀ in XLR:**

1. ♀ carrier + affected ♂
2. Turner
3. Lyonization

	X-linked Dominant	X-linked Recessive
<b>Affected Individual</b>	<ul style="list-style-type: none"> <li>May be homo-, hetero- or hemi-</li> <li>One parent must be affected (except for new mutation)</li> </ul>	<ul style="list-style-type: none"> <li>Homozygous ♀ or hemizygous ♂</li> <li>Affected ♂ Mother is obligate carrier</li> <li>Affected ♀: When?</li> </ul>
<b>Sex</b>	Heterozygous ♀ is affected	Heterozygous ♀ is carrier (♂ > ♀)
<b>Carrier</b>	No carrier state	Carrier (phenotypically normal ♀) No carriers in ♂ (hemizygous)
<b>Transmission</b>	Vertical (No skipping)	Transverse (skipping)
<b>Offsprings</b>	<ul style="list-style-type: none"> <li>Homozygous ♀ → 100% affected</li> <li>Heterozygous ♀ → 50% affected</li> <li>Hemizygous ♂ → 100% of ♀-affected 0% of ♂ affected (<b>none...</b>)</li> </ul>	<ul style="list-style-type: none"> <li>Heterozygous ♀ (carrier) → 50% of sons affected 50% of daughters carrier</li> <li>Affected ♂ Hemizygous → 100% of daughters carrier 0% of sons affected (<b>none...</b>) i.e., all are phenotypically normal</li> </ul>
<b>Examples</b>	Hypophosphatemic rickets Alport syndrome Incontinentia pigmenti	Hemophilia A & B, G-6-PD deficiency, Duchenne, Hunter, Color blindness, Menkes, Fabry, Nephrogenic DI, CGD Lesch-Nyhan, Wiskott-Aldrich, Fragile X
<b>Pedigree</b>	$\begin{array}{ccc} \underline{XX} & X & XY \\ & \swarrow & \searrow \\ \underline{XX} & \underline{XY} & \underline{XX} & \underline{XY} \\ & \underbrace{\hspace{1cm}} & \underbrace{\hspace{1cm}} \\ & 50\% & 50\% \\ & \text{Affected} & \text{Normal} \end{array}$	$\begin{array}{ccc} \underline{XX} & X & XY \\ & \swarrow & \searrow \\ \underline{XX} & \underline{XX} & \underline{XY} & \underline{XY} \\ & \underbrace{\hspace{1cm}} & \underbrace{\hspace{1cm}} \\ & 25\% & 25\% \\ & \text{Carrier} & \text{Affected} \end{array}$

## B) Multifactorial (Polygenic)

**Definition:** It is interaction between polygenic & environmental factors

### Characteristics:

1. Familial
2. Has sex preference (CHPS is more common in ♂)
3. RR is the same for relatives who share equal proportion of genes (1<sup>st</sup> degree relatives)
4. RR is ↑↑ in consanguineous parents
5. RR is ↑↑ if the relationship to affected relative is close
6. RR is ↑↑ if the disease in the affected relative is more severe
7. RR is ↑↑ if more than one close relative is affected
8. RR is ↑↑ if there is affection of the less frequently affected sex (♀ relative with CHPS)
9. The concordance rate in monozygotic twins is not 100% (20-60%)
10. The concordance rate in dizygotic twins is 2-4% (similar to ordinary siblings)

**Examples:** CHD, CHPS, DDH, talipes, spina bifida, DM, obesity, HTN, epilepsy, asthma



## C) Non-Traditional Inheritance

### 1. Mitochondrial (Cytoplasmic)

- ☑ Mitochondrial DNA (discuss)
- ☑ The ♂ child of affected mother does not transmit the trait

Post-fertilization event

### 2. Mosaicism

**Definition:** It is the presence of  $\geq 2$  different cell lines derived from 1 fertilized ovum

**Types:**

#### a. Somatic cell mosaicism:

- Gene mutation in somatic cells
- The mutation is transmitted to daughters cells not to offsprings "Non-heritable"
- Serious if it occurs early in embryogenesis

#### b. Germ cell mosaicism:

- Gene mutation in germ cells
- The mutation is transmitted to offsprings "heritable"
- Diagnosis is difficult (Suspected when more than one affected child is born)

### 3. Uniparental disomy (UPD)

**Definition:** It is the inheritance of 2 homologous chromosomes (or 2 copies of gene) from one parent

**Types:**

#### a. Isodisomy: Duplication of a chromosome in case of monosomy

#### b. Heterodisomy: Loss of a chromosome in case of trisomy

**Significance:** a child may be affected with AR trait if only one parent is carrier (isodisomy)

**Examples:**

- ☑ Prader-Willi syndrome occurs due to:  
Deletion\* of paternally acquired segment of chromosome 15  
Or maternal disomy (both chromosomes 15 are from the mother)
- ☑ Angelman syndrome occurs due to:  
Deletion\* of maternally acquired segment of chromosome 15  
Or paternal disomy (both chromosomes 15 are from the father)
- ☑ Cystic fibrosis: 1/500 of cases are due to UPD (del F508)
- ☑ Beckwith Wiedmann syndrome

Normally the 2 copies of most genes are functionally equivalent

### 4. Genomic imprinting

**Definition:** It is different gene expression depending on the parent of origin of such genes

**Mechanism:** Inactivation (imprinting) of genes occurs through methylation

**Examples:**

- ☑ Prader-Willi & Angelman: chromosome 15 is dependent on parental origin
- ☑ Huntington chorea: if the gene is transmitted from the father → severe juvenile form
- ☑ Myotonic dystrophy: " " " " " the mother → severe congenital form

### 5. Pronuclear transplantation

- ☑ Experimentally in mice
  - Zygote formed of 2 sets of paternal chromosomes → well developed placenta & membranes  
Poor development of embryonic structures
  - Zygote formed of 2 sets of maternal chromosomes → well developed embryonic structures  
Poor development of placenta & membranes
- ☑ In humans
  - 2 sets of paternal chromosomes → Hydatidiform mole (placental tumor)
  - 2 sets of maternal chromosomes → Teratoma (embryonic tumor)
  - 2 sets paternal + 1 maternal → Large placenta + IUGR
  - 2 sets maternal + 1 paternal → Small placenta + IUGR (placental insufficiency)

## 6. Foreign gene expression

If a foreign gene is inserted very early in the embryo, it will be transmitted to offsprings  
But expressed only if it was transmitted from the father

## 7. Triplet Repeat Expansion disorders

**Definition:** Diseases caused by expansion of the number of 3-base-pair repeats (e.g., CGG)

**Mechanism:** expansion of the number is a dynamic process through successive generations

**Examples:**

- ☒ Fragile X syndrome (XL-R)
- ☒ Huntington chorea (AD)
- ☒ Myotonic dystrophy (AD)

Anticipation

# Variation in Gene Expression

## 1. Penetrance

The proportion of individuals with a particular genotype to have the corresponding phenotype  
Examples: Achondroplasia, Hereditary spherocytosis

## 2. Expressivity

Variation in the severity of expression of a particular gene  
Examples: Osteogenesis imperfecta, Hereditary spherocytosis

## 3. Anticipation

The tendency of some diseases to have an earlier onset & / or increased severity with successive generations

Examples: Huntington chorea, Myotonic dystrophy

## 4. Pleiotropy

Multi-system affection in spite of single gene affection  
Examples: Galactosemia, Tuberous sclerosis

## 5. Heterogeneity

The same C/P is caused by affection of more than one gene (each one can cause the disease)  
Examples: Homocystinuria

## 6. Multifactorial Inheritance

The interaction between polygenic & environmental factors  
Examples: CHD, CHPS, DDH, talipes, spina bifida, DM, obesity, HTN, epilepsy, asthma

## 7. Gene Interaction

The expression of one gene is affected by the presence of other genes  
Examples: Bombay phenotype of blood groups

## 8. Linkage

The co-segregation of 2 non-allelic genes which have their loci very close to each other on the same chromosome & so they move together during meiosis  
Examples: Genetic markers used in detection of a particular gene

## 9. Sex influences

The effect of the gender on the C/P of some diseases  
Examples: XL diseases

## 10. Variation of Age of Onset

The variation in the onset of presentation of some diseases  
Examples: Myotonic dystrophy (Early), Huntington chorea (Late), Hemochromatosis (Late)

### Control of gene expression

- ☒ TATA & CCAAT boxes
- ☒ Enhancers & Silencers
- ☒ Intronic sequence
- ☒ Methylation of genes
- ☒ Sequence 3' to the gene

# Genetic Engineering

## Recombinant DNA Technology

### Definition

It is the science that deals with the detailed **structure** of genes together with their normal physiological **function**, pathological **defects** & possible **treatment**. It usually involves the formation of recombinant DNA molecule

### Recombinant DNA

It is the creation of a new DNA by cutting of DNA segment from parent genome & joining it to another DNA molecule (Vector)

Requirements: 2 Enzymes; restriction endonuclease, DNA-ligase, Vector, Bacteria for cloning

### Vector

It is a DNA molecule used to carry DNA region of interest

Type	Nature	Can carry up to
Plasmid	<ul style="list-style-type: none"> <li>▪ Small <u>extra-chromosomal</u> <u>circular</u> <u>double</u> stranded DNA molecules</li> <li>▪ Found in bacterial cells, but multiply independent on the cell</li> <li>▪ Carry some genes (e.g., antibiotic resistance...)</li> </ul>	10 Kb
Phage	Virus that infects bacteria	20 Kb
Cosmid	Plasmid containing part of phage	50 Kb

### Restriction Endonucleases

Bacterial DNA is methylated

- ☒ These are **bacterial** enzymes
- ☒ Restriction: they **restrict** the multiplication of bacteriophage viruses in the bacterial cells
- ☒ Endonucleases: they **cut** in the **middle** of the polynucleotide chain at specific sequences
- ☒ Restriction (recognition) sites: **specific** sequence at which cutting occurs. Restriction sites are usually **symmetrical** e.g., 5' GAATTC 3' [Madam = I'm Adam]
- ☒ Products of restriction enzymes: Fragments with different length with sticky or blunt ends
- ☒ Number: > 2000 enzymes have been isolated
- ☒ Examples: EcoRI, Mst II...

### Ligase

It is an enzyme which can join 2 DNA molecules usually derived from bacteria (E.coli)

### Technique

#### I) Preparation of gene:

1. Intact genes: using restriction enzymes → large fragments with large number of genes
2. Synthesis of DNA from mRNA (complementary DNA = cDNA)
 

mRNA → <sup>Reverse transcriptase</sup> cDNA (single strand) → Double stranded DNA

This DNA contains only the coding sequence (No introns- No regulatory elements)
3. Chemical synthesis: for small genes

#### II) Formation of Recombinant DNA

1. Separation of the **plasmid** from host cell (bacteria)
2. **Opening** of the circular DNA of the plasmid by a restriction enzyme
3. **Human DNA** is also broken by the same restriction enzyme & the part containing the required gene is separated
4. **Insertion** of the separated gene into the plasmid
5. The **circle** is reformed by the enzyme DNA ligase (chimeric molecule is formed)
6. The plasmid is reinserted into the **bacterial cell**
7. **Culture** on a medium containing antibiotic to which plasmid is resistant

8. Selective growth & multiplication of bacteria containing the recombinant plasmid
9. The bacteria can also produce human **protein** coded by the human gene
10. **Extraction** of plasmid from bacterial cell
11. **Opening** of the plasmid by a restriction enzyme
12. Separation of multiple copies of human DNA (**synthesis of DNA probes**)

## DNA Probes

### Definition

It is a labeled single-stranded DNA fragment which can hybridize specifically with complementary sequences helping in their identification. Labeling is done by fluorescence or radioactive  $^{32}\text{P}$

### Types

- ☒ Gene specific probes
- ☒ Complementary DNA-(cDNA) probes
- ☒ Synthetic probes

### Synthesis

Recombinant DNA technology

## Applications of Recombinant DNA Technology

1. Gene structure, function & mapping
2. Diagnosis of genetic diseases (& understanding of pathogenesis) ➡
3. Clinical genetics
  - ☒ Prenatal diagnosis
  - ☒ Presymptomatic diagnosis
  - ☒ Carrier detection
4. Synthesis of genetically engineered vaccines
5. Biosynthesis of: Insulin, GH, EPO, Factor VIII, GM-CSF, Interferon
6. Gene therapy
7. Agriculture??

#### Examples of diseases:

1.  $\beta$ -Thalassemia
2. Sickle cell
3. Cystic fibrosis
4.  $\alpha_1$ -antitrypsin deficiency
5. Gaucher
6. Tay-Sachs

## Genetically engineered vaccines

**Advantages** Low cost No contamination  $\uparrow\uparrow$  Antigenicity  $\downarrow\downarrow$  potential infectivity

### Strategies

Strategies for live attenuated vaccines	Strategies for live inactivated vaccines
<b>A) DNA modification</b> <ul style="list-style-type: none"> <li>▪ Attenuation of the organism, followed by:</li> <li>▪ Genetic modification preventing reversion to the wild virulent form</li> </ul> <b>B) Recombinant viruses</b> <ol style="list-style-type: none"> <li>a. Recombinant Influenza vaccine</li> <li>b. Recombinant vaccinia virus vaccine</li> </ol> <ul style="list-style-type: none"> <li>▪ Removal of the non essential DNA sequences of vaccinia virus and</li> <li>▪ Replacing them by certain genes responsible for antigenicity of other pathogens</li> <li>▪ Single vehicle <math>\rightarrow</math> vaccines against many pathogens</li> </ul>	<b>A) Synthetic peptide</b> <p>Use of short segment of the protein (rather than the entire molecule) as the immunogen</p> <b>B) Recombinant HBV vaccine</b> <ul style="list-style-type: none"> <li>▪ Isolation of the viral gene coding for HBsAg</li> <li>▪ Insertion into baker's yeast</li> <li>▪ Synthesis of <math>\uparrow\uparrow</math> amount of HBsAg</li> <li>▪ Purification</li> <li>▪ Inactivation with formalin</li> <li>▪ Adsorption on <math>\text{Al}(\text{OH})_3</math></li> <li>▪ Storage at <math>2-8^\circ\text{C}</math></li> </ul>

# Diagnosis of Genetic Diseases & DNA Polymorphism

## Isolation

1. Type of the cell: WBC, lymphocytes, skin fibroblasts, amniocytes, chorionic villi cells
2. Detergent + cell [Dissolves lipids]
3. Sodium dodecyl sulphate (SDS) [Liberates proteins]
4. Shaking with Phenol [Coagulates proteins]
5. Ethyl alcohol [Precipitates DNA]

## Techniques (All are done using specific probes) ———

### 1. Blotting & Hybridization

It allows visualization of a specific fragment

#### Types:

- ☒ Southern blotting for DNA
- ☒ Northern blotting for RNA
- ☒ Western blotting for Proteins

In Southern blotting, the DNA is first digested by specific restriction enzyme into fragments

→ Gel electrophoresis into bands → Addition of specific DNA probes to the bands

→ Detection of complementary strands in the sample (if present)

#### **Disadvantages:**

1. Long time
2. Large amount is needed
3. Radioactivity

### 2. Polymerase Chain Reaction (PCR)

It allows massive amplification of a specific DNA segment. PCR is done in cycles

One segment can be amplified up to 1 million within 2-3 hours

#### Requirements:

- Thermostable DNA polymerase
- 2 Oligonucleotide primers (20-30 nucleotide long) that can hybridize to complementary sequences on the DNA strands (one primer for each DNA strand) flanking the area of DNA to be amplified
- Nucleotides

#### Cycles:

- **Denaturation:** Heating of the sample (95° C) to separate DNA strands
- **Annealing:** The 2 primers are added + cooling (to allow hybridization)
- **Extension:** Extension of the primers along the 2 DNA strands leading to duplication of the segment of interest
- **Cycles are repeated:** 25-35 times

**Product:** If there is mutation of the target DNA, amplification can still occur (further analysis)

### 3. Ligase Chain Reaction (LCR)

It allows massive amplification of a specific DNA segment like PCR. It is done in cycles.

It is a process of ligation & not extension

#### Requirements:

- Thermostable DNA ligase
- 4 Oligonucleotide primers (20-30 nucleotide long) that can hybridize to complementary sequences on the DNA strands (2 primers for each DNA strand)
- Nucleotides

#### Cycles:

- **Denaturation:** Heating of the sample (95° C) to separate DNA strands
- **Annealing:** The 4 primers are added + cooling (to allow hybridization)
- **Ligation:** Ligation of the 2 primers along the DNA strand
- **Cycles are repeated:** 25-35 times

**Product:** If there is mutation of the target DNA, amplification can not occur (except with specific primers)

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- **Annealing:** The 4 primers are added + cooling (to allow hybridization)
- **Ligation:** Ligation of the 2 primers along the DNA strand
- **Cycles are repeated:** 25-35 times

**Product:** If there is mutation of the target DNA, amplification can not occur (except with specific primers)

#### 4. DNA Sequencing

Determination of the exact sequence of nucleotides in the DNA molecule

- 4 reaction tubes are used, to each a mixture of "nucleotides & DNA polymerase" is added
- One dideoxynucleotides of either (A,T,G,C) as chain terminator is added to each tube
- Each tube will contain sequences of different lengths but all terminate with a particular ddNTP
- Electrophoresis of these fragments will help in the detection of the exact sequence

#### 5. Allele Specific Oligonucleotide Probe Analysis (ASO)

Two synthetic oligonucleotides are synthesized one for the normal & the other for mutant gene

- Homozygous normal individual → Hybridization only with normal oligonucleotide
- Homozygous diseased individual → Hybridization only with mutant oligonucleotide
- Heterozygous individual → Hybridization with both normal & mutant oligonucleotides

#### 6. Single Stranded Complementary Polymorphism

It allows rapid screening of a specific gene or DNA variation (polymorphism)

#### 7. Restriction Fragment Length Polymorphism

##### Rationale:

- Restriction endonucleases cut the DNA at specific sequences (restriction sites) → Large number of restriction fragments of different lengths
- Any change in the sequence within the restriction site will block cutting → change of the fragment length

##### Example:

- Mst II is a restriction endonuclease that cuts the DNA at  $\beta^6$  position
- Mutation causing sickle cell changes the sequence at the restriction site [GAG → GUG]
- Normal individuals → 1.1 Kb restriction fragments
- Sickle cell anemia → 1.3 Kb restriction fragments



#### 8. Indirect DNA Diagnosis (Linkage)

- The use of a genetic marker (e.g., DNA polymorphism...) to identify a specific gene
- It requires a family with more than one affected member
- Markers that are closely linked to the affected gene are found much more common in the affected members (diseased)
- Markers that are not associated with the disease are randomly shared between affected & unaffected members of the families

#### 9. Amplification Refractory Mutation System (ARMS)

##### Rationale:

- PCR amplifies both normal & mutant genes (further analysis is needed)
- ARMS is allele specific PCR (amplification of a specific allele)

##### Requirements:

Three oligonucleotide primers are synthesized:

1. One for the normal gene
2. One for mutant gene
3. One is constant & attached to the other complementary DNA strand

Two tubes are used:

1. Tube (A): 1 + 3
2. Tube (B): 2 + 3

##### Results:

- Amplification in tube (A) only → Homozygous normal individual
- Amplification in tube (B) only → Homozygous diseased individual
- Amplification in tube (A) & (B) → Heterozygous individual

	PCR	LCR
Primers	2 primers (one on each DNA strand)	4 primers (2 on each DNA strand)
Process	Extension	Ligation
Amplification	Normal & Mutant genes (except ARMS)	Normal genes (except if specific primers are used)

# Cytogenetics

## Definition

It is the study of chromosomes: No., size, shape, structure, inheritance & abnormalities

## Techniques

### 1. Chromosomal Banding

Staining of chromosomes: G banding (Giemsa stain) Q banding (quinacrine)

### 2. FISH (Fluorescence In Situ Hybridization)

It is fluorescence labeled DNA probes which can hybridize specifically with complementary sequences helping in their identification. It is used to study:

- ☒ Complete chromosomes: Trisomy 21
- ☒ Chromosomal subregions
- ☒ Microdeletion syndromes (*Mention*)

### 3. Multicolored FISH (M-FISH)

Using different fluorochromes

### 4. Comparative Genomic Hybridization (CGH)

It finds differences in gene copy number by comparing one genome to another

#### Technique:

- Reference DNA: Labeled with fluorescence (Red)
- Test DNA: Labeled with fluorescence (Green)
- Mixture of both is added to normal DNA (Not labeled with fluorescence)
- Green/Red ratio is measured on each chromosome

#### Results:

- Region of amplification in test DNA → Excess of green fluorescence [e.g., Tumor cells...]
- Region of deletion in test DNA → Excess of red fluorescence [e.g., Deletion syndromes...]
- If test & reference DNA are equally represented → Green: red ratio = 1:1 "Yellow"

### 5. Different Display Analysis

It demonstrates difference in gene products between normal & abnormal cells

### 6. DNA Microarray Technology

Computer analysis of genes

## Human Genome Project

No. of human genes ~ 25,000

## Definition

It is an organized coordinated effort to *map & sequence* all the human DNA

Started in 1990, the first map released in 1994 (linkage map)

The final version 2004 (covers 99% of the human genome with 99.9% accuracy)

## Goals of HGP



### **Goals of HGP:**

1. Physical map of chrom...
2. Complete a genomic map
3. Find all genes
4. Sequence of all genes
5. Acquire the genome as colonies

## Different Maps

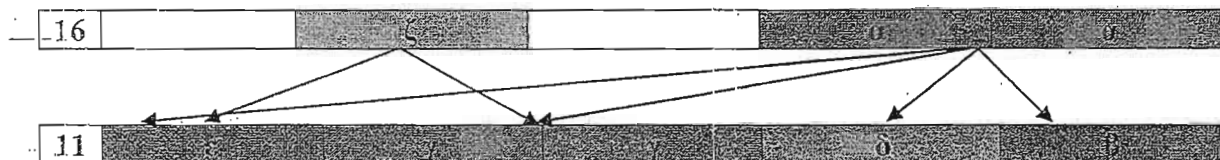
1. **Chromosomal Map:** The number, size & shape of chromosomes in the human cell
2. **Physical Map:** Staining of chromosomes: G banding & Q banding
3. **Linkage Map:** Determine the relative location of genetic markers (*Definition of linkage??*)
4. **cDNA Map:** Shows the position of exons along the DNA
5. **Macrorestriction Map:** Cutting of human DNA with restriction endonucleases into large fragments which are ordered & subdivided into small pieces to be mapped



# Genetic Control of Hemoglobin

## Physiology

- Hemoglobin is formed of:
  - Heme (= iron  $\text{Fe}^{++}$  protoporphyrin): Not genetically determined
  - Globin: 4 polypeptide chains ( $2\alpha + 2\text{non } \alpha$ ); each chain contains a heme group
- Globin part is genetically determined. Two families of genes are responsible:
  - $\alpha$ -Gene family ( $2\alpha$  genes & 1  $\zeta$  gene)  $\rightarrow$  141 aa
  - $\beta$ -Gene family ( $\beta$  gene,  $\delta$  gene, 2  $\gamma$  genes &  $\epsilon$  gene)  $\rightarrow$  146 aa



## Normal Hemoglobin

Normal Hb	Name	Structure
Embryonic Hb	Gower I	$2\zeta + 2\epsilon$
	Gower II	$2\alpha + 2\epsilon$
	Portland	$2\zeta + 2\gamma$
Fetal Hb	Hb F	$2\alpha + 2\gamma$
Adult Hb	HbA	$2\alpha + 2\beta$
	HbA <sub>2</sub>	$2\alpha + 2\delta$

- Zeta ( $\zeta$ ) & Epsilon ( $\epsilon$ ) genes stop working by the 3<sup>rd</sup> month of pregnancy
- By the 3<sup>rd</sup> month of pregnancy, Hb F is the major Hb

	At Birth	6-12 months
Hb A	20-30 %	97-98 %
Hb F	70-80 %	0-2 %
Hb A <sub>2</sub>	-	2-3.4 %

## Abnormal Hemoglobin

Abnormal Hb	Structure
Hb S	$2\alpha + 2\beta^{6\text{ valine}}$
Hb C	$2\alpha + 2\beta^{6\text{ lysine}}$
Hb D	Variable
Hb E	$2\alpha + 2\beta^{26\text{ lysine}}$
Hb H	$4\beta$
Hb-Barts	$4\gamma$
Hb M	$\uparrow\uparrow$ tendency to oxidation ( $\uparrow\uparrow$ Met Hb formation)
Hb Lepore	Fusion of $\beta$ & $\delta$ genes
Hb constant spring	$\uparrow\uparrow$ $\alpha$ chain by extra 31 aa (sense mutation)

- During fetal life & early childhood, HbF & HbA ( $\beta$  &  $\gamma$ ) are inversely proportionate
- 3 months before birth,  $\downarrow\downarrow$   $\gamma$  &  $\uparrow\uparrow$   $\beta$  synthesis (*Hb switch*)

## Classification of Hb Disorders

### A) Qualitative (Hemoglobinopathy) [Structural defects]

#### a. Point Mutation

- ☒ Sickle cell anemia Hb S

- Homozygous SS (*sickle cell anemia*): [ $2\alpha + 2\beta^{6\text{ valine}}$ ] No HbA, HbS 80-95, HbF 2-20%.
- Heterozygous AS (*sickle cell trait*): [ $2\alpha + \beta + \beta^{6\text{ valine}}$ ] HbA 60 % & HbS 40 %

- ☒ Hb C [ $2\alpha + 2\beta^{6\text{ lysine}}$ ]

- ☒ Hb E [ $2\alpha + 2\beta^{26\text{ lysine}}$ ]

- ☒ Hb M [*Tyrosine instead of histidine*]

#### b. Deletion: Hb Lyon (Short $\beta$ chain)

#### c. Insertion: Hb Grady (Long $\alpha$ chain)

#### d. Unequal crossing-over: Hb Lepore (Fusion of $\beta$ & $\delta$ genes)

#### e. Chain termination: Hb constant spring (sense mutation $\rightarrow$ $\alpha$ -chain with extra 31 aa)

## B) Quantitative [ $\downarrow\downarrow$ formation of $\alpha$ or $\beta$ chains]

### a. $\beta$ Thalassemia [ $\downarrow\downarrow$ formation of $\beta$ chains]

$\beta^0$  = absent  $\beta$ -chain synthesis     $\beta^+$  = reduced  $\beta$ -chain synthesis

- Homozygous (*Thalassemia major*): [ $\beta^0 \beta^0$  or  $\beta^+ \beta^+$ ] HbF >70%, Normal Hb A<sub>2</sub>
- Heterozygous (*Thalassemia minor*): [ $\beta^0 \beta^0$  or  $\beta^+ \beta^+$ ]  $\uparrow\uparrow$  Hb A<sub>2</sub> (3.4-7 %) &  $\uparrow\uparrow$  Hb F (2-6 %)

#### Genetics:

- *Point mutation*: affecting transcription, mRNA splicing or translation
- *Deletion*: of  $\beta$  gene
- *Hb Lepore*: Fusion between  $\beta$  and  $\delta$  genes (unequal crossing-over)

### b. $\alpha$ Thalassemia [ $\downarrow\downarrow$ formation of $\alpha$ chains]

#### Genetics:

- *Deletion*: of one or more of the 4  $\alpha$  genes (silent carrier, trait, HbH, hydrops fetalis)
- *Chain terminator defect*: sense mutation (Hb Constant Spring)

Hb A is *absent* in  $\beta^0$  thalassemia & *decreased* in  $\beta^+$  thalassemia

Syndrome	# Gene	Genotype	Hematological	C/P	Hb
$\alpha$ -Silent carrier	1	- $\alpha$ / $\alpha$ $\alpha$	Normal	Normal	Neonate: Hb Barts (1-2 %)
$\alpha$ -Thalassemia trait	2	- $\alpha$ /- $\alpha$ or -/- $\alpha$ $\alpha$	Microcytosis Hypochromia	Normal Mild anemia	Neonate: Hb Barts (5-10 %)
HbH disease	3	- $\alpha$ / - -		Mild H. anemia	Neonate: Hb Barts (20-30 %)
Hydrops fetalis	4	- - / - -	Anisocytosis Poikilocytosis	Death IU or Early neonatal	Neonate: Hb Barts (80-90 %)

*HbH disease*: mild to moderate hemolytic anemia + Splenomegaly + Jaundice

Adults have HbH ( $\beta_4$ ). Transfusion is usually not required

- c. **Hereditary persistence of fetal Hb (HPFH)**: failure of switch from  $\gamma$  to  $\beta$  chain commonly caused by deletion of  $\beta$  and  $\delta$  genes

## Genetic Control of Blood Groups

### 1. Major Blood Groups (ABO system)

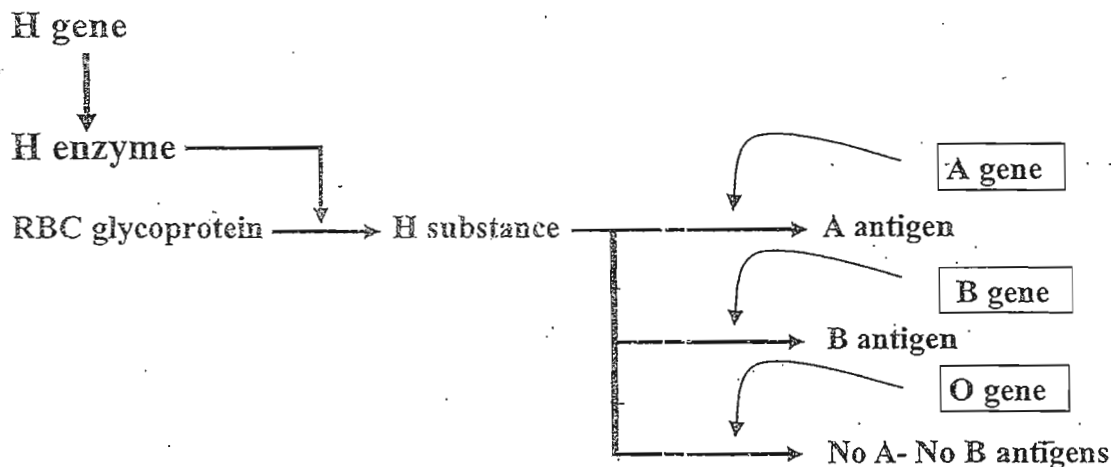
- ABO locus: One locus with 4 different alleles ( $A_1$ ,  $A_2$ , B, O) on chromosome 9
- $A_1$  is dominant over  $A_2$
- O is recessive
- A & B are codominant
- Antibodies (agglutinins) against ABO system are naturally occurring & of IgM type

**Codominance** = Both alleles are expressed in the heterozygous

Phenotype	Genotype	Antigens	Antibodies	Frequency (UK)
A	Homo- $A_1A_1$ , $A_1A_2$ , $A_2A_2$	A	Anti-B	45
	Hetero- $A_1O$ , $A_2O$			
B	Homo- BB	B	Anti-A	8
	Hetero- BO			
O	OO	-	Anti-A & Anti-B	44
AB	AB	A, B	-	3

#### Biosynthesis of ABO Antigens:

- ABO antigens are formed from H substance by enzymes coded by A or B genes. O gene is completely inactive (leaves H substance unaltered)
- H substance is formed from a glycoprotein precursor by the H enzyme encoded by H gene
- H gene is dominant over h gene
- Bombay phenotype: Individuals with homozygous (hh)  $\rightarrow$  No H enzyme  $\rightarrow$  No H substance  $\rightarrow$  No formation of A or B antigens (This person will have O blood group irrespective to his genotype)



### Secretion of Blood group substances:

- ABO antigens are secreted in body fluid (saliva, tears, breast milk...)
- Secretion depends on Se gene
- Se gene is dominant over se gene
- Secretors are either homozygous (Se/Se) or heterozygous (Se/se)
- Non-secretors are homozygous (se/se)

Anti-D Abs occur with sensitization

1. Blood transfusion
2. Pregnancy, abortion or delivery

## 2. Rh Blood Group system

- The Rh system is controlled by 3 pairs of alleles, the most important is D & d alleles
- D allele is dominant over d (DD & Dd are Rh positive)
- Other alleles are C, c, E, e
- Antibodies against Rh system (*Anti-D Antibodies*) are Not naturally occurring & of IgG type

## 3. Other Blood Group systems

- Kell system
- Kidd system
- Duffy system
- Lewis system

## Hemolytic Disease of the newborn (see Neonatology)

1. Rh incompatibility
2. ABO incompatibility
3. Minor blood group incompatibility (Kell, Kidd, Duffy)

# Genetic Background of Inborn Errors of Metabolism

## A) Enzyme Defects

**Enzymes:** Biological catalysts. Virtually all enzymes are proteins (either simple or conjugated). Conjugated enzyme (holoenzyme) = Apoenzyme + Coenzyme

**Apoenzyme:** It is the protein part of the holoenzyme

**Coenzyme:** It is the organic non-protein part of the holoenzyme (e.g., vitamin...)

- ☒ Enzyme defect may be:
  - Genetically determined
  - New mutation
- ☒ This may lead to:
  - ↓↓ Enzyme synthesis
  - ↓↓ Enzyme activity due to: Distortion of enzyme configuration  
↓↓ Affinity of the apoenzyme to substrate or coenzyme
- ☒ Enzyme defect leads to metabolic block:
  - a. Accumulation of precursors

Disease	Enzyme Defect	Accumulated substance
Galactosemia	Galactose-1-P-uridyltransferase	Galactose & Galactitol
GSD (Von Gierke)	Glucose 6-Phosphatase	Glycogen
Gaucher	Glucocerebrosidase ( $\beta$ -Glucosidase)	Glucocerebrosides (glycolipid)
Niemann-Pick	Sphingomyelinase	Sphingomyeline
MPS (Hurler)	$\alpha$ -L- Iduronidase	GAG = Glycosaminoglycan
GM <sub>1</sub> Gangliosidosis	$\beta$ -Galactosidase	Gangliosides
GM <sub>2</sub>	Tay-Sachs	Hexosaminidase A
	Sandhoff	Hexosaminidase A & B

### b. Deficiency of end-product

Albinism: (↓↓ Melanin) Tyrosine  $\xrightarrow{\text{Tyrosinase}}$  Melanin

### c. Opening of alternative pathway

Normally: Phenylalanine  $\xrightarrow{P.\text{hydroxylase}}$  Tyrosine  
 Phenylketonuria: ↑↑ Phenylalanine  $\rightarrow$  ↑↑ Phenylpyruvate, lactate & acetate

## B) Transport across cell membranes

### a. Transport across cell membrane

Specific Vit. B<sub>12</sub> malabsorption due defective receptors for IF-B<sub>12</sub> complex

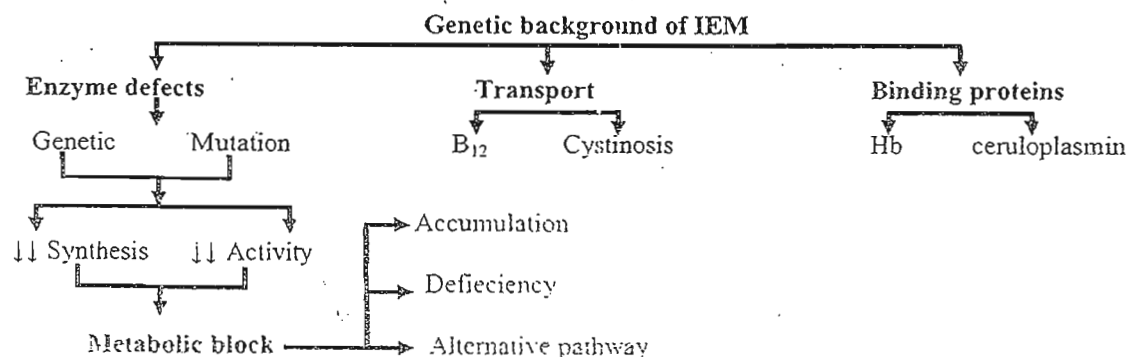
### b. Transport across lysosomal membrane

Cystinosis: Trapping of cystine inside the lysosomes. [Action of Cysteamine??]

## C) Binding Proteins

a. Hemoglobin carries O<sub>2</sub>: HbM cannot carry O<sub>2</sub>

b. Ceruloplasmin carries Copper: Wilson disease



# Twin Studies

(Multiple Pregnancies)

## Incidence

- **Twins** = 1: 86      **Triplets** = 1: 86<sup>2</sup>      **Quadruplets** = 1: 86<sup>3</sup>
- 1/3 of twins are monozygotic (MZ) = Uniovular = Identical
- 2/3 of twins are dizygotic (DZ) = Binoovular = Non-identical

Chorion is formed around D<sub>3</sub>  
Amnion is formed around D<sub>8</sub>

## Etiology

- ☑ Monozygotic twins: develop from splitting of a single zygote (single fertilized ovum)

Splitting	Freq.	Placenta	Chorion	Amnion	Cords	Fern
1 <sup>st</sup> 3 days	25 %	2	2	2	—2	Dichorionic-diamniotic
Days 4-8*	75 %	1	1	2	2	Monochorionic-diamniotic
Days 9-15	-	1	1	1	—2	Monorionic-monoamniotic
> D 15	-	1	1	1	2	Conjoined twins

Conjoined twins (Craniopagus, thoracopagus...)

- ☑ Dizygotic twins: develop from 2 fertilized ova [2 ova + 2 sperms]  
Always Dichorionic-Diamniotic

## Definitions

**Concordance:** Both members have the same trait

**Discordance:** Only one co-twin has the trait (i.e., Different from his partner)

**Monozygotic twins:** have the same genotype (one fertilized ovum)

So any difference in phenotype must be due to environmental factors

**Dizygotic twins:** have different genotypes (two fertilized ova)

So any difference in phenotype may be due to environmental or genetic factors

## Genetic Applications

- If the concordance rate of a specific disease in MZT is > DZT → genetic factors
- If the concordance rate of a specific disease in DZT of the same sex is > DZT of different sex → sex effect
- Concordance rate for type 2 DM in MZT is almost 100%
- Concordance rate for type 1 DM in MZT is 30-50%
- Concordance rate for DM in MZT is > DZT
- Concordance rate for CF in MZT is almost 100% (*purely genetic*)
- Concordance rate for SLE in MZT is 50% & 5% in DZT (*Not only genetic*)

Genetic component is stronger in type 2 DM

Type	MZT	DZT
<b>Etiology</b>	Splitting of a single zygote (One ovum)	Develop from 2 fertilized ova
<b>Placenta &amp; Fetal membrane</b>	<ul style="list-style-type: none"> <li>▪ 75% are (Monochorionic-diamniotic): [1 Placenta + 1 Chorion + 2 Amnions]</li> <li>▪ 25% are (Dichorionic-diamniotic): [2 Placentas + 2 Chorions + 2 Amnions]</li> </ul>	Always Dichorionic-diamniotic [2 Placentas + 2 Chorions + 2 Amnions]
<b>Sex</b>	The same	May be different
<b>Hair</b>	The same color & texture	"
<b>Eye</b>	The same color	"
<b>Blood group</b>	The same	"
<b>HLA group</b>	The same	"
<b>Skin grafts</b>	Well accepted	Rejected if different HLA
<b>Dermatoglyphics</b>	Homolateral hands are more similar than both hands of the same co-twin	Homolateral hands are less similar than both hands of the same co-twin

# Genetic Counseling

## Definition (Talking to the family)

It is a **communication** process offered to high risk or affected individual to understand the nature of a genetic disease, its transmission & the options available for management. It should be neutral & non-directive. The counselor should provide support to the family to cope with decisions taken.

## Requirements

- Accurate **family history & pedigree** (including all relatives, abortions...)
- Full confirmed **diagnosis**
- Reviewing the updated medical, laboratory & genetic **information** about the disorder including the mode of inheritance & RR

## Indications of Genetic Counseling

- Advance parental age
  - ☒ Maternal age > 35 yrs
  - ☒ Paternal age > 50 yrs
2. Consanguinity
3. Spontaneous abortion
4. Congenital malformation & dysmorphology
5. Developmental delay & mental retardation
6. Atypical (ambiguous) genitalia
7. Disorders of sex development (complete androgen insensitivity...)
8. Short stature (♀)
9. Primary amenorrhea
10. Infertility
11. +Ve Antenatal screening tests
  - ☒ +Ve maternal serum screening test (e.g., triple test)
  - ☒ +Ve US screening test
  - ☒ Fetal karyotype & sex??
12. Teratogen exposure (Drug, substance or exposure...)
13. Heterozygote screening based on ethnic risk (Carrier detection)
  - ☒ Sickle cell anemia [Africa]
  - ☒ Tay-Sachs, Gaucher, Canavan [Jewish]
  - ☒ Thalassaemia [Mediterranean]
14. Adult-onset genetic disease
  - ☒ Huntington chorea
  - ☒ Malignancy: (Breast, ovarian, colon...)

### Common situations of Genetic Counseling:

- ☒ Prenatal diagnosis [?Abortion]
- ☒ Newborn with congenital anomalies [?Support]
- ☒ Later in life [?Premarital ?Prenatal]

## Recurrence Risk

- Single gene inheritance: (Give examples on AD, AR, Sex-linked)
- Multifactorial inheritance: 2-4 %

## Diagnostic problems

- Heterogeneity: The same C/P is caused by affection of more than one gene (Each one can cause the disease), with *different* modes of inheritance. Examples: Homocystinuria, MPS
- Phenocopies: Conditions similar to genetic diseases but they are caused by environmental factors [e.g., Microcephaly...]
- Sporadic cases (Common in modern families). The disorder may be:
  - ☒ Non-genetic
  - ☒ Chromosomal (↓↓ RR = 1 %)
  - ☒ Multifactorial (RR = 2-4%)
  - ☒ AR (normal parents) "RR = 25%"
  - ☒ AD (new mutation) "RR = 1%"
  - ☒ XLR (new mutation or carrier mother)

# Dysmorphism

## Definition

It is a morphological developmental abnormality of **prenatal** onset

2-4% of newborn babies have a physical anomaly

## Classification

- A) Single primary defects\*: More common, usually multifactorial
- B) Multiple malformation syndromes: One or more developmental abnormalities affecting 2 or more systems. It is usually due to chromosomal abnormalities or teratogenic exposure

## Single primary defects

### A) Malformation

- Localized error in morphogenesis
- Examples: CHD (RR = 2-5%), polydactyly, CL ± P

Fetal movement is an important factor in the development of the MSK System

### B) Deformation

- Alteration in the shape or structure of a normally-differentiated organ
- It usually affects the musculoskeletal system (e.g., Talipes...)
- It is due to ↓↓ fetal movement
  - a. **Intrinsic factors (Fetal neuromuscular apparatus):**
    - CNS: developmental defects
    - Motor unit: Muscles: Congenital myopathy (nemaline rod), Myotonic dystrophy
    - Nerves: SMA type 1 (Werdnig-Hoffmann)
  - b. **Extrinsic factors:**
    - Oligohydramnios
    - Multiple pregnancies
    - Malpresentation (Breech)
    - Uterine shape: Bicornuate or septate uterus
    - Uterine tumors: Fibroid

### C) Disruption

- Destruction of a previously normal part
- Destruction may be mechanical, vascular, infectious
  - **Mechanical:** Amniotic bands → Amputation of a digit
  - **Vascular:** Interruption of blood supply leads to ischemic infarction
  - Examples: Mesenteric → Intestinal atresia & CNS → Porencephaly (brain cyst)
  - **Infectious:** TORCH infection

### D) Sequence

- Single primary defect results in a cascade of subsequent events
- Although there are multiple anomalies, it is considered as a single primary defect
- Example: Pierre-Robin syndrome
  - The single primary defect is mandibular hypoplasia →
  - Dropping of the tongue backwards → "U-shaped" Cleft palate

### o Syndrome

- Multiple malformations that occur together due to a single known underlying cause
- Example: Down syndrome

### o Association

- Multiple malformations that occur together in a **non-random** manner, usually due to unknown cause
- Example: VATER/VACTERL association

**VATER/VACTERL:**  
Vertebral, Anorectal, Cardiac, Trachea, Esophagus, Renal, Limb



# Teratogens

## Definition

Teratogen is any **environmental** agent (drug, substance or exposure) that interferes with normal **embryonic** development (Structure, growth or function)

### Examples:

- Drugs: Alcohol, captopril, cocaine, indomethacin, lithium, phenytoin, propranolol, streptomycin, tetracycline, thalidomide (phocomelia), warfarin... (See Neonatology)
- Infection
- Maternal DM & PKU
- Radiation (ionizing & non-ionizing)

### Mechanism of teratogens

1. DNA damage
2. Cell death
3. Vascular insult
4. Delayed differentiation

## Effect

The effect depends on:

- ☑ Nature of the teratogen (*The mechanism is usually unknown*)  
Warfarin is teratogenic on fetal cartilages [# carboxylation of glutamic acid]
- ☑ Time of exposure (fetal age)
  - a. Weeks 1-3 (embryonic stage): All or none fashion; either killing or no effect
  - b. Weeks 3-10 (organogenesis): organs are most susceptible to damage
  - c. Weeks 10-40 (fetal growth & maturation): ↓↓ risk but may interfere with function
- ☑ Genetic predisposition: teratogens are not universal "Pharmacogenetics"

## Prevention

- Avoid drugs, infection & radiation
- Control of maternal DM, PKU
- Abortion

# Pharmacogenetics

## Definition

It is the genetically determined variations in drug metabolism & response

Pharmacogenetic variability is the cause of the observed wide range of drug response

### Examples:

- Exaggerated physiologic effect
- Drug resistance
- Drug side effects

Pharmacogenetics will help to identify  
"The right drug for the right patient"

Half-lives of several drugs are more similar in MZT > DZT "Genetic factors"

## Factors affecting the response to drugs

- ☑ Genetic factors "Pharmacogenetics"
- ☑ HLA typing
- ☑ Physiologic factors (age, sex, pregnancy)  
Chloramphenicol (usual dose) → **Gray baby syndrome** in *premature & newborn* infants
- ☑ Environmental factors (Diet, smoking)
- ☑ Route of administration
- ☑ Organ failure (Liver & Kidney)
- ☑ Drug interaction
  - Valproate → ↑↑ toxicity of Phenytoin, Phenobarbital & Lamotrigene
  - Diuretics → ↑↑ Digitalis toxicity
  - Aminoglycosides + frusemide (vancomycin & amphotericin B) → ↑↑ Nephrotoxicity
  - Antacids → ↓↓ Absorption of steroids, NSAIDs & iron
- ☑ Patient compliance

### Drug metabolism (Biotransformation)

Phase I (Oxidation, Reduction, Hydrolysis)

Phase II (Conjugation) with:

- Glucuronic acid: Chloramphenicol, Paracetamol
- Acetic acid: Isoniazide, sulfonamides
- Glycine: aspirin



## A) Effects of genes on drug metabolism

### 1. Acetylation

Individuals homozygous for "slow acetylation" polymorphism are more susceptible to:

- Isoniazide (INH) toxicity "peripheral neuritis"
- Sulfonamides induced Stevens-Johnson syndrome

CYPs are heme-containing enzymes

### 2. Polymorphism in Cytochrome P<sub>450</sub>

- CYPs are the most important enzymes of phase I biotransformation
- Fetal expression is limited, functional activity is acquired postnatally (4 months- 4 years)
- Enzyme activity can be induced or inhibited by various agents
- They are grouped into:

Families (1, 2, 3...) → Subfamilies (A, B, C...) → Members (1, 2, 3...)

- CYPs genes are highly polymorphic (↑↑ alleles) → Individual variation in drug metabolism

	Drug substrates	Inducers	Inhibitors
<b>CYP<sub>1A2</sub></b> (4 months)	<ul style="list-style-type: none"> <li>▪ Acetaminophen</li> <li>▪ Theophylline</li> <li>▪ Caffeine</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cigarette smoke</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cimetidine</li> </ul>
<b>CYP<sub>2D6</sub></b> (4 years)	<ul style="list-style-type: none"> <li>▪ Codeine</li> <li>▪ Haloperidol</li> <li>▪ Captopril</li> <li>▪ Propranolol</li> </ul>	<ul style="list-style-type: none"> <li>---</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cimetidine</li> <li>▪ Quinidine</li> </ul>
<b>CYP<sub>3A4</sub></b> (1 year)	<ul style="list-style-type: none"> <li>▪ Acetaminophen, Theophylline</li> <li>▪ Cyclophosphamide, cyclosporine</li> <li>▪ Erythromycin</li> <li>▪ Verapamil</li> </ul>	<ul style="list-style-type: none"> <li>▪ Phenytoin</li> <li>▪ Phenobarbitone</li> <li>▪ Rifampicin</li> </ul>	<ul style="list-style-type: none"> <li>▪ Erythromycin</li> <li>▪ Fluconazole</li> </ul>

3. Alcohol dehydrogenase polymorphism: Individual variation in response to ethanol

4. HLA type: ↑↑ Some drug toxicity in certain HLA types (↑↑ gold toxicity in HLA-DRW<sub>3</sub>)

## B) Effects of drugs on certain genetic diseases

### 1. G6PD Deficiency (XL-R)

There are > 100 enzyme variants of G6PD

G-6-PD B<sup>+</sup> is the normal enzyme

G-6-PD A<sup>+</sup> is a normal variant

G-6-PD B<sup>-</sup> (5-40 % activity)

G-6-PD A<sup>-</sup> (5-15 % activity) } Abnormal variants

Hemolysis occurs in patients with G-6-PD deficiency on exposure to certain drugs (oxidant stress)

Agents precipitating hemolysis in G6PD deficiency:

2. Fava beans
3. Antibiotics: sulfonamides, chloramphenicol, nitrofurantoin
4. Antimalarial: primaquine
5. Aspirin, Vit K
6. Chemicals: Benzene, naphthalene

### 2. Malignant hyperthermia

AD condition due to mutation of Ca ion release channels

C/P: Malignant hyperthermia in response to halothane or succinylcholine

### 3. Pseudocholinesterase (serum cholinesterase)

Individuals with ↓↓ enzyme activity develop prolonged paralysis in response to succinylcholine (*succinylcholine apnea*)

Types of cholinesterase enzymes:

True CE: Endogenous A.Ch.  
Pseudo CE: Exogenous A.Ch.  
Succinyl choline

### 4. Acatalasia

Individuals with absent catalase enzyme activity develop methemoglobinemia in response to oxidant stresses (Due to accumulation of H<sub>2</sub>O<sub>2</sub>)



# Gene Therapy

## Definition

It is transfer of recombinant DNA into human cells for correction of a disease

## Requirements

1. **Preparation of gene** (*How? See Recombinant DNA*)
2. **Vector (viral\* or non-viral)**: It is a DNA molecule used to carry DNA region of interest
3. **Human cell**: transfer & integration of the gene can be directed to:
  - ☒ Somatic cell: Not heritable
  - ☒ Germ cell: Heritable to successive generations (Ethically not accepted)

## Principle

1. Gene is attached to the vector
2. Transfection of the human cell by the vector
  - ☒ Ex vivo gene delivery: Cells are taken from the patient, gene is inserted & returned back
  - ☒ In vivo gene delivery: Direct transfection of the human cell (e.g., portal v for liver cells)
3. The delivered gene is incorporated into the nucleus
4. Transcription of the delivered gene into mRNA
5. Translation into the deficient protein "Therapy"
6. The formed protein may act in the target cell or secreted to exert effect in distant cells

## Fate of the delivered gene

1. Degradation by lysosomes: No effect
2. Permanent expression: Gene is integrated into the human DNA, so transmitted to daughter cells
3. Transient expression : Maintained in the nucleus as an episome, so it is active in such cell only but not transmitted to daughter cells

## Applications of Gene Therapy

- ☒ Treatment of genetic diseases (ADA deficiency...)
- ☒ Treatment of acquired diseases (Infectious diseases "HIV", malignancy...)

Gene therapy remains experimental

# Vector Systems

## Ideal Vector

- Reaches the target cells by **in vivo administration**
- **Single administration**
- **Integrated safely** in the genome (without disturbing normal genes)
- Not integrated in **oncogenic sites**
- Removes the **defective gene** & replaces it with normal gene
- **Transmitted** to daughter cells "permanent expression"

## Classification

### A) Viral vectors

1. Retrovirus
2. Adenovirus
3. Adeno-associated virus

### B) Non-viral vectors

1. Naked (Plasmid)
2. Liposomes
3. Ligands

## Risks of Viral Vectors (*All viral vectors*)

- Insertional mutations (random integration into normal genes)
- Infectious complications due to activation of the recombinant virus into the wild form
- Inflammatory & Immune responses

## A) Viral vectors (*These viruses require genetic modification of the wild form*)

### 1. Retrovirus

a. **Wild virus:** Replication occurs as follow

- ☒ Attachment through specific receptors (CD<sub>4</sub> on T<sub>H</sub> cells in cases of HIV infection)
- ☒ Endocytosis & Eclipse
- ☒ Reverse transcription

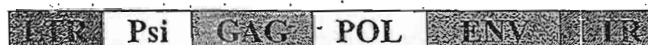
Viral RNA  $\xrightarrow{\text{Reverse transcriptase}}$  DNA (single strand)  $\rightarrow$  ds DNA  $\rightarrow$  integrated into human DNA

- ☒ Transcription into mRNA
- ☒ Translation & production of viral proteins (Viral capsid & enzymes)
- ☒ Capsidation (assembly)
- ☒ Release

#### Viral Genome contains the following genes:

1. GAG gene: codes for capsid proteins
2. POL: codes for reverse transcriptase
3. ENV: codes for envelope proteins
4. Psi  $\psi$  sequence: important for packaging events
5. LTR (Long terminal repeats): powerful promoters

Packaging = Integration + formation of viral particles



### b. Recombinant virus

☒ Recombinant virus contains:

1. Psi  $\psi$  sequence
2. LTR

3. Therapeutic gene replacing GAG, POL, ENV (So it is a defective virus)

☒ GAG, POL & ENV genes from a helper virus (No Psi  $\psi$ ) are permanently integrated in the genome of packaging cell lines

☒ The recombinant virus is transfected into the packaging cell

☒ The recombinant virus uses proteins encoded by the packaging cell genome to produce viral particles which contain only therapeutic gene (No GAG, POL & ENV genes).

☒ These new viral particles are not infectious

☒ Transfection of target human cell by the recombinant virus (*How? 2 methods*)

☒ Integration of the therapeutic gene (*Mention the fate?*)



## 2. Adenovirus & adenoassociated virus

Type	Advantages	Limitations
<b>Retrovirus</b> Small virus RNA virus	<ul style="list-style-type: none"> <li>▪ Permanent expression (Integration)</li> <li>▪ Transmitted to daughter cells</li> </ul>	<ul style="list-style-type: none"> <li>▪ Only small gene can be used (9 Kb)</li> <li>▪ Integration depends on cell division</li> <li>▪ Ineffective in resting cells</li> </ul>
<b>Adenovirus</b> Big virus DNA virus	<ul style="list-style-type: none"> <li>▪ Large gene can be used (39 Kb)</li> <li>▪ Effective in resting cells (non-dividing)</li> <li>▪ Effective in Rx of acquired condition (malignancy)</li> <li>▪ Effective in Rx of genetic respiratory diseases (CF). Tendency to infection of cells lining airways</li> </ul>	<ul style="list-style-type: none"> <li>▪ Transient expression (No Integration)</li> <li>▪ No transmission to daughter cells</li> <li>▪ Episomal particle</li> <li>▪ Regular multiple administration</li> <li>▪ Inflammatory reaction</li> </ul>
<b>Adeno-associated virus</b> Defective virus DNA virus	<ul style="list-style-type: none"> <li>▪ Effective in resting cells (non-dividing)</li> <li>▪ Wild virus has site specific integration on chromosome 19 (not recombinant one)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Only small gene can be used (&lt; 5 Kb)</li> <li>▪ Transient expression (No Integration)</li> <li>▪ It is defective virus (coinfection with adenovirus)</li> </ul>

Mention risks of viral vectors (I I I I)

## B) Non-Viral vectors

### 1. Naked DNA (Plasmid DNA)

Small, extra-chromosomal, circular dsDNA molecules found in bacteria

#### Advantages:

- Easy production in large amount
- Large gene can be used (10 Kb)

### 2. Liposomes

- Incorporation of plasmid into small lipid vesicle → ↑↑ delivery to target cell
- Liposomes fuse with cell membrane of target cell → Internalization
- Lysosomal digestion of lipid & release of DNA into the nucleus
- The recombinant DNA is maintained as episome (Transient expression)

### 3. Ligands

- Linkage of plasmid to a protein conjugate
- The protein helps to direct the plasmid DNA to specific cell containing specific receptors

## Immune Reaction against vectors

- ☒ Cell mediated immunity: Cytotoxic T cells react against vector & formed gene product
- ☒ Humoral immunity: Neutralizing Abs against the vector (# subsequent transfection)

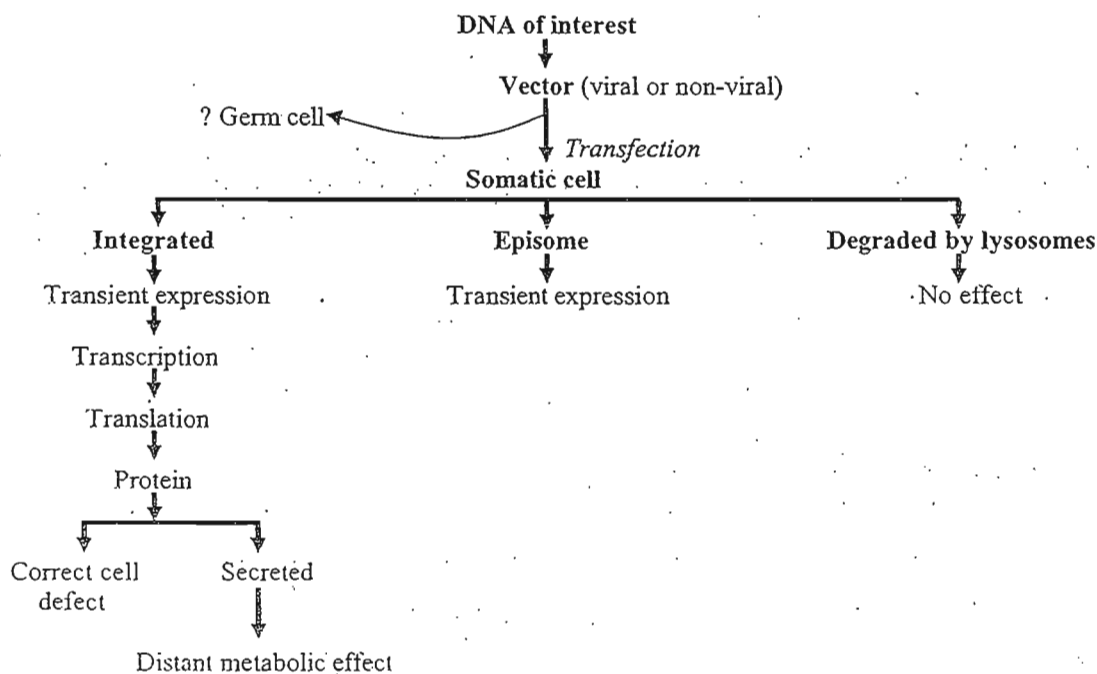
## Alternative strategies for gene therapy

**Organoids:** Ex vivo genetically altered cells to produce specific gene product

These cells are returned back to the patient & placed SC, in BV, peritoneal cavity  
Produce Factor VIII (Hemophilia),  $\beta$ -Glucuronidase (Type VII MPS)...

## Diseases targets for Gene Therapy

- Gene therapy remains experimental & challenging
- Many common diseases, such as HTN & DM are caused by combined effect of many genes and so are not candidate for gene therapy (*at least now*)
- The first human gene therapy trial was in ADA deficiency in 1990 (relatively small gene)



# Prevention of Genetic Diseases

## A) Epidemiology

- Genetic registry & counseling (Carrier detection)
- Identification of mutagens

## B) Prenatal Diagnosis

### 1. Maternal serum $\alpha$ -fetoprotein (MSAFP)

- ☒  $\downarrow\downarrow$  MSAFP: Down syndrome & other trisomies
- ☒  $\uparrow\uparrow$  MSAFP: Neural tube defects (anencephaly, encephalocele, spina bifida)

Hydrocephalus

GIT: TOF, Intestinal atresia

Renal: Congenital nephrosis, Obstructive uropathy

Twins, IUFD

### 2. Fetal US

- ☒ Assessment of fetal growth, gestational age & well-being
- ☒ Nuchal Translucency thickening (NT): thickening of the fat pad at the back of the neck
- ☒ Dilated cerebral ventricular system (hydrocephalus)
- ☒ Dilated renal pelvicalyceal system [large UB in PUV]
- ☒ Absent stomach (TOF), Double-bubble (duodenal atresia), Distended loops (IO)
- ☒ Fetal echocardiography

### 3. Amniocentesis & Chorionic Villus Sample (CVS)

	Amniocentesis	Chorionic villus sample
<b>Timing</b>	2 <sup>nd</sup> Trimester (14-16 weeks of gestation)	1st Trimester (9-12 weeks of gestation)
<b>Anesthesia</b>	LA or GA	LA or GA
<b>Technique</b>	Transabdominal sample of amniotic fluid (US guided)	Transvaginal or Transabdominal biopsy of chorionic villi (US guided)
<b>Obtained Cells</b>	<b>1. Fetal sexing</b> (XL diseases e.g., hemophilia, Duchenne ...) <b>2. Karyotyping</b> (chromosomal abnormalities e.g., Down, trisomies...) <b>3. DNA analysis</b> (Thalassemia, Sickle cell disease, cystic fibrosis...) <b>4. Enzyme assay</b> (Galactosemia, GSD, Gaucher, Niemann-Pick, MPS, GM <sub>1</sub> , GM <sub>2</sub> )	
<b>Liquid phase</b> (in amniocentesis)	<b>1. <math>\alpha</math>-fetoprotein</b> (causes as MSAFP) <b>2. Bilirubin</b> (erythroblastosis fetalis) <b>3. Lung maturity</b> (L/S ratio...) <b>4. Renal maturity</b> (creatinine) <b>5. CAH</b> ( $\uparrow\uparrow$ Ketosteroids) <b>6. Congenital hypothyroidism</b> ( $\downarrow\downarrow$ T <sub>4</sub> )	??
<b>Complications</b>	<ul style="list-style-type: none"> <li>▪ Abortion</li> <li>▪ Fetal injury</li> <li>▪ Hemorrhage</li> <li>▪ Rh sensitization</li> <li>▪ Infection (amnionitis)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Abortion (2% higher)</li> <li>▪ Amnion puncture</li> <li>▪ Hemorrhage</li> <li>▪ Rh sensitization</li> <li>▪ Infection</li> </ul>
<b>Pros &amp; Cons</b>	<ul style="list-style-type: none"> <li>▪ Less risk of abortion</li> <li>▪ Technically easier</li> <li>▪ <math>\downarrow\downarrow</math> yield of cells (cells must be cultured)</li> </ul>	<ul style="list-style-type: none"> <li>▪ <math>\uparrow\uparrow</math> yield of cells (rapid diagnosis)</li> <li>▪ Early in pregnancy (when termination is less risky &amp; less emotionally traumatic)</li> </ul>

### 4. Fetoscopy & Fetal Tissue Sampling

Transabdominal introduction of fetoscope under LA (US guided), 2<sup>nd</sup> trimester

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Complications	■ Abortion ■ Fetal injury ■ Hemorrhage ■ Rh sensitization ■ Infection (amnionitis)	■ Abortion (2% higher) ■ Amnion puncture ■ Hemorrhage ■ Rh sensitization ■ Infection
Pros & Cons	■ Less risk of abortion ■ Technically easier ■ $\downarrow\downarrow$ yield of cells (cells must be cultured)	■ $\uparrow\uparrow$ yield of cells (rapid diagnosis) ■ Early in pregnancy (when termination is less risky & less emotionally traumatic)

### 4. Fetoscopy & Fetal Tissue Sampling

Transabdominal introduction of fetoscope under LA (US guided), 2<sup>nd</sup> trimester

- a. Direct visualization (structural anomalies e.g., phocomelia, neural tube defects...)
- b. Cordocentesis (Fetal blood sampling)
  - Hemoglobinopathies: Sickle cell anemia
  - Coagulation disorders (Hemophilia)
  - Neonatal alloimmune thrombocytopenia
  - Fetal infection (Toxoplasmosis)
  - Immunodeficiency
  - Karyotyping, DNA analysis & enzyme assay
- c. Fetal liver biopsy (PKU & OTC deficiency)
- d. Fetal skin biopsy (Epidermolysis bullosa)

**OTC** = Ornithine transcarbamoylase  
Most common type of urea cycle defects  
XL-R    الوحيد

### C) Pre-implantation genetic diagnosis (PGD)

#### Definition

Diagnosis of genetic diseases before pregnancy is established  
Must be preceded by IVF & ICSI

**Blastomeres:** Cells formed by cleavage of the zygote. Each one contains the full genetic material of the baby

#### Technique

- ☒ Stimulation of maternal ovulation ( )
- ☒ Ovum retrieval
- ☒ Fertilization by sperm (Intracytoplasmic sperm injection)
- ☒ Embryo is cultured till the stage of 6-8 blastomeres
- ☒ Single blastomere is separated from the embryo (micromanipulation technique)
- ☒ Genetic make-up is determined [Each blastomere contains the full genetic material]
- ☒ The remaining blastomeres are left intact & allowed to grow (if no disease)
- ☒ Transfer to mother's uterus (Usually 3 non-affected embryos are transferred)

#### Methods of Diagnosis

- a. Karyotyping (important in XL-R diseases when the exact mutation is unknown)  
Only ♀ zygotes are transferred to the mother's uterus
- b. PCR & ARMS
  - Detection of a specific disease
  - Amplification of DNA followed by analysis e.g., DNA sequencing
- c. FISH:

Complete chromosomes  
Chromosomal subregions  
Microdeletion syndromes

#### Advantages of PGD

- a. Very early (!! Before pregnancy, so avoids emotional trauma)
- b. Couples who are carriers of AR genetic diseases can have healthy children

#### Diseases which can be detected by PGD

- ☒ Chromosomal: Trisomies (21; 18; 13), Turner, Klinefelter
- ☒ AR: Cystic fibrosis, Tay-Sachs, (? Gaucher)
- ☒ XL-R: Hemophilia, Duchenne, Fragile X

### D) Screening of Genetic Diseases

1. **Neonatal screening:** Congenital hypothyroidism, PKU, Galactosemia, Sickle, CF, MC
2. **Heterozygote screening** based on ethnic risk (Carrier detection)
  - ☒ Sickle cell anemia [Africa]
  - ☒ Tay-Sachs, Gaucher, Canavan [Jewish]
  - ☒ Thalassemia [Mediterranean]
3. **Carrier detection** in relatives of affected individuals
4. **Screening for at risk population** (Screening for hyperlipidemia to detect persons at risk of ischemic heart disease)

# Treatment of Genetic Diseases

## 1. Gene therapy (*Give examples*)

## 2. Enzyme Induction

Phenobarbitone in Crigler-Najjar syndrome type II (AD)

## 3. Enzyme Replacement

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Gaucher disease             | <input checked="" type="checkbox"/> ADA deficiency  |
| <input checked="" type="checkbox"/> Pompe disease (GSD-type II) | <input checked="" type="checkbox"/> Some MPS        |
| <input checked="" type="checkbox"/> Fabry disease               | <input checked="" type="checkbox"/> Cystic fibrosis |

## 4. Recombinant proteins

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> GH          | <input checked="" type="checkbox"/> EPO        |
| <input checked="" type="checkbox"/> Insulin     | <input checked="" type="checkbox"/> GM-CSF     |
| <input checked="" type="checkbox"/> Factor VIII | <input checked="" type="checkbox"/> Interferon |

## 5. Replacement of Hormones

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Hydrocortisone (CAH)             | <input checked="" type="checkbox"/> GH (Hypopituitarism)                  |
| <input checked="" type="checkbox"/> 9- $\alpha$ fludrocortisol (CAH) | <input checked="" type="checkbox"/> Thyroxine (Congenital hypothyroidism) |

## 6. Replacement of vitamins

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> B <sub>1</sub> (Maple syrup urine disease) | <input checked="" type="checkbox"/> Biotin (Propionic acidemia)             |
| <input checked="" type="checkbox"/> B <sub>6</sub> (Homocystinuria)            | <input checked="" type="checkbox"/> Folic acid (Megaloblastic anemia)       |
| <input checked="" type="checkbox"/> B <sub>12</sub> (Methylmalonic acidemia)   | <input checked="" type="checkbox"/> Vitamin D (Vitamin D resistant rickets) |

## 7. Dietary restriction

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Maple syrup urine (V I L)   | <input checked="" type="checkbox"/> Urea cycle disease (proteins)     |
| <input checked="" type="checkbox"/> Methionine (Homocystinuria) | <input checked="" type="checkbox"/> Galactosemia (galactose, Lactose) |
| <input checked="" type="checkbox"/> PKU (Phenylalanine)         | <input checked="" type="checkbox"/> Hypercholesterolemia (Lipids)     |

## 8. Induction of alternative pathways

Na benzoate in urea cycle defects (to eliminate NH<sub>3</sub>)

## 9. Preventive therapy

Avoidance of certain drugs in G6PD deficiency

## 10. Removal of abnormal tissue

- Splenectomy (Hereditary spherocytosis)
- Colectomy (Polyposis coli)

## 11. Transplantation

Renal transplantation for management of polycystic kidneys (PKD)

## 12. Portocaval anastomosis

In cases of portal hypertension (GSD type IV)

## 13. Extracorporeal therapy

Plasmapheresis in the Rx of hypercholesterolemia



# Polymorphism & Genetic Markers

People are genetically very similar (99.9% identical)

## Polymorphism

- Genetic differences between individuals which provides variation within a species
- The occurrence of 2 or more alleles at a locus in a frequency greater than that can be maintained by mutation alone
- Polymorphisms are more common in the non-coding regions of DNA
- Polymorphisms in the coding regions of DNA are responsible for:
  - ☒ Variation in blood-groups
  - ☒ Variation in HLA typing
  - ☒ Variation in drug metabolism (pharmacogenetics)
  - ☒ Variation in enzyme activity (There are > 100 enzyme variants of G6PD enzyme)

## Clinical Importance of Polymorphism

1. Blood grouping & Tissue typing (HLA)
2. Pharmacogenetics
3. Forensic medicine
4. Problems with identity, zygosity, paternity (DNA finger printing)
5. Genetic markers (Linkage studies)
6. Some diseases occur in a polymorphic frequencies
  - ☒ Sickle cell anemia } Heterozygous shows mild manifestations
  - ☒ Thalassaemia } while homozygous is severe

Most polymorphisms produce no clinical phenotype

## Forms & Diagnosis of Polymorphism

### A) DNA technology

1. RFLP: When variations of DNA sequence involve restriction sites  
Detected by Southern blotting technique
2. PCR
3. DNA sequencing
4. Single nucleotide polymorphism (SNP): Different people have a different nucleotide at a given location on a chromosome
5. VNTR (Variable numbers of tandem repeats):

Pre-axial: Radial or tibial  
Post-axial: Ulnar or fibular

### B) Altered gene products

1. Variation in blood groups & HLA typing
2. Variation in enzyme activity due to altered protein structure (altered activity, thermostability or electrophoretic properties)

### C) Physical features: Post-axial polydactyly

### D) Chromosomal heteromorphism (= Structural polymorphism in chromosomes)

1. Variation in the size of Y chromosome
2. Variation in the fragile sites

## Repeated sequences in Human DNA

	Repeat size (bp)	Total size (kb)	Features
Satellite	5-200	100	
Minisatellite	10-60	20	2 families: VNTR & telomeric family
Microsatellite	1-4	1	Repeats of A, CA

(VNTR = Variable numbers of tandem repeats)

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(VNTR = Variable numbers of tandem repeats)

## Genetic Marker

It is a simple inherited genetic trait (e.g., DNA polymorphism\*, biochemical marker, blood group...) that can be linked to a disease locus, so can be used for diagnosis & gene mapping

## Linkage

The co-segregation of 2 non-allelic genes which have their loci very close to each other on the same chromosome & so they move together during meiosis

## Linkage analysis (Indirect DNA Diagnosis)

- The use of a genetic marker (e.g., DNA polymorphism...) to identify a specific gene
- It requires a family with more than one affected member
- Markers that are not associated with the disease are randomly shared between affected & unaffected members of the family
- Markers that are closely linked to the affected gene are found much more common in the affected members (diseased)

## Clinical Importance of Linkage

1. Determination of the genotype
2. Determination of the mode of inheritance
3. Gene mapping
4. Prenatal diagnosis
5. Presymptomatic diagnosis
6. Carrier detection
7. Determination of genetic factors in complex traits (e.g., DM)

Genetic markers that are usually used are:

1. SNPs
2. Microsatellites

## Gene mapping

### Definition

Assignment of genes to specific loci

### Methods

1. Linkage studies
  - It requires a family with more than one affected member (Family study)
  - It is a measure of genetic distance
2. Somatic cell genetic method
  - Cells lacking specific chromosomal segment lack a specific gene
  - Cells having specific chromosomal segment show a specific gene
3. Cytogenetic study
 

FISH: directly visualizes the specific gene
4. Gene dosage studies
  - Amount of gene product (protein) is directly proportionate to the number of copies
  - Normal = amount of protein
  - Trisomy =  $1\frac{1}{2}$  amount of protein
  - Monosomy =  $\frac{1}{2}$  amount of protein

### Importance

1. Understand the anatomy of the human genome
2. Understand the function of the human genome
3. Gene therapy
4. Analysis of heterogeneity

<p><b>Question 80 of 124</b></p> <p>A. Autosomes B. Aneuploidy C. Triploidy D. Mosaic E. Chimera F. Trisomy G. Monosomy</p> <p>H. Instructions: Match the above terms with their correct description from the list below:</p> <ol style="list-style-type: none"> <li>1. An entire half set of chromosomes</li> <li>2. Two different cell lines derived from a single zygote</li> <li>3. Three copies of one chromosome</li> <li>4. Chromosomes 1-22</li> <li>5. Two different cell lines caused by the fusion of two zygotes</li> <li>6. An extra or missing chromosome</li> </ol>	<p><b>Question 81 of 124</b></p> <p>All the following statements about mitochondrial inheritance are true except:</p> <ol style="list-style-type: none"> <li>A. Transmission occurs through the maternal line</li> <li>B. Sperm has negligible amount of mitochondrial DNA</li> <li>C. Is seen in some types of diabetes mellitus and deafness</li> <li>D. Both sexes may be affected</li> <li>E. Daughters of affected males are obligate carriers</li> </ol>
<p><b>Question 82 of 124</b></p> <p>One of the following statements about consanguinity is incorrect:</p> <ol style="list-style-type: none"> <li>A. Is seen more commonly in certain ethnic groups</li> <li>B. Presence of consanguinity favours autosomal recessive (AR) inheritance</li> <li>C. Two brothers marrying two sisters is an example</li> <li>D. The rarer the disorder, the higher will be the proportion of affected individuals due to parental consanguinity</li> <li>E. Increases the likelihood of birth defects only slightly</li> </ol>	<p><b>Question 83 of 124</b></p> <p>A young couple attend your clinic for genetic counselling. There is a history of phenylketonuria on the husband's side of the family and they have questions about the disorder and its inheritance. Which of the following statements about PKU is false?</p> <ol style="list-style-type: none"> <li>A. The inheritance is autosomal recessive</li> <li>B. PKU is classically due to deficiency of the enzyme phenylalanine hydroxylase</li> <li>C. Mental retardation is only apparent after a few months</li> <li>D. Over 50% of affected infants have EEG abnormalities</li> <li>E. Serum tyrosine levels are typically low</li> </ol>
<p><b>Question 84 of 124</b></p> <p>All of the following statements about Glucose-6-phosphate dehydrogenase deficiency are false except:</p> <ol style="list-style-type: none"> <li>A. Is more common in women than in men.</li> <li>B. Is caused by mutations of the G6PD gene on chromosome 4.</li> <li>C. Often leads to chronic haemolysis.</li> <li>D. Requires treatment with desferrioxamine to prevent iron overload.</li> <li>E. Is associated with haemolytic crises induced by sulfonamides.</li> </ol>	<p><b>Question 85 of 124</b></p> <p>The following are true of autosomal dominant (AD) inheritance pattern except:</p> <ol style="list-style-type: none"> <li>A. Both males and females are equally affected</li> <li>B. Achondroplasia and Marfan syndrome are common examples</li> <li>C. Late onset disorders are usually inherited in an AD pattern</li> <li>D. Both parents are usually asymptomatic carriers</li> <li>E. Variable expression occurs frequently</li> </ol>

**Question 86 of 124**

- A. 45, X
- B. 47, XYY
- C. 47, XXY
- D. 47, XX+21
- E. 47, XX+13
- F. 47, XXX
- G. 47, XX+18

Instructions: Match the following karyotypes with the correct phenotype from the list below:

1. Normal male with extra Y chromosome
2. Female with Down syndrome
3. Normal female with extra X chromosome
4. Male with Klinefelter syndrome
5. Female with Turner syndrome
6. Female with Patau syndrome

**Question 88 of 124**

A child has had his chromosomes analysed in the course of various investigations and the result is: 46 XY, t (2;5)(q35;p21.3).

Which of the following statements is correct?:-

- A. He has more than 46 chromosomes
- B. The result shows all his genetic defects
- C. There is a translocation between the short arm of chromosome 2 and the short arm of chromosome 5
- D. He is likely to be infertile
- E. There is an increased risk of him having a child with difficulties

**Question 90 of 124**

- A. Chromosome
- B. Chromatid
- C. Centromere
- D. Autosome
- E. Gene
- F. Chromatin

Choose the most likely definitions for each of the above from the list given below:

1. Central constriction of a chromosome, separating the short (p) and long (q) arms
2. One of two parallel identical strands of a chromosome, seen during mitosis and meiosis
3. Thread-like packages of genes seen in the nucleus of a cell
4. A specific sequence of DNA that encodes for a protein or polypeptide chain
5. Each of the first 22 pair of chromosomes except the sex chromosomes

**Question 87 of 124**

A 56 year old lady brings her 15 year old son to see the GP. The boy complains of burning pains in his hands and feet that can be debilitating at times. He is noted to have a diffuse red skin rash, particularly over his trunk and back. His mother has been diagnosed with hypertrophic cardiomyopathy.

What is the most likely diagnosis?:-

- A. Tay-Sachs disease
- B. Fabry's disease
- C. Homocysteinuria
- D. Neimann-Pick disease
- E. Tangier disease

**Question 89 of 124**

An 11-year-old boy has a long history of recurrent chest infections and poor weight gain. Which of the following findings is least likely to support a diagnosis of cystic fibrosis?

- A. Sweat Na concentration of 93 mmol/l
- B. Sinusitis
- C. Peribronchial thickening on CXR
- D. A sweat Na greater than sweat Cl
- E. Metabolic alkalosis

**Question 91 of 124**

- A. Trisomy
- B. Triploidy
- C. Aneuploidy
- D. Monosomy
- E. Translocation
- F. Inversion

Instructions: Match the above options with the correct definition from the choices given below:-

1. A missing chromosome in each cell
2. An extra chromosome in each cell
3. An extra set of the total haploid genome
4. Intra-chromosomal rearrangements
5. Inter-chromosomal rearrangements

<p><b>Question 92 of 124</b></p> <p>A. Autosomal dominant B. Autosomal recessive C. X linked recessive D. Teratogenic E. Mitochondrial</p> <p>Instructions: One of the above options best describes the pattern of inheritance of the disorders given below. Please note that the options above can be used for more than one disorder:-</p> <ol style="list-style-type: none"> <li>1. Duchenne muscular dystrophy</li> <li>2. Huntington disease</li> <li>3. Cystic fibrosis</li> <li>4. Phenylketonuria</li> <li>5. Marfan syndrome</li> <li>6. Fetal alcohol syndrome</li> <li>7. Leber's hereditary optic neuropathy (LHON)</li> </ol>	<p><b>Question 93 of 124</b></p> <p>The following statements are correct about autosomal recessive inheritance pattern except:-</p> <ol style="list-style-type: none"> <li>A. One or more affected children can be born to unaffected parents</li> <li>B. There is a higher incidence of consanguinity</li> <li>C. For carrier parents with one affected child the chance of having another affected baby is 1 in 4 (25%)</li> <li>D. Males and females are affected with equal frequency and severity</li> <li>E. Male to male transmission is noted</li> </ol>
<p><b>Question 94 of 124</b></p> <p>A. 46,XY B. 47, XXY – C. 45, X D. 47, XYY E. 47, XX+ 18 F. 47, XX+13</p> <p>Instructions: Match the above karyotypes with the correct description from the list given below:-</p> <ol style="list-style-type: none"> <li>1. Female with Patau syndrome</li> <li>2. Female with Edward syndrome</li> <li>3. Turner syndrome</li> <li>4. Normal male karyotype</li> <li>5. Klinefelter syndrome</li> </ol>	<p><b>Question 95 of 124</b></p> <p>All the following statements about Turner syndrome are true except:-</p> <ol style="list-style-type: none"> <li>A. Dorsal oedema (puffiness of hands and feet) may be the only presenting feature in the newborn period</li> <li>B. Growth hormone has been successfully used to improve final adult height</li> <li>C. Infertility is almost universal in Turner syndrome</li> <li>D. Mental retardation is a common feature</li> <li>E. Almost 99% of fetuses with 45,X karyotype are spontaneously aborted in early pregnancy</li> </ol>

<p><b>Question 101 of 124</b></p> <ul style="list-style-type: none"> <li>A. Imprinting disorders</li> <li>B. Uniparental disomy</li> <li>C. Gonadal mosaicism</li> <li>D. Mitochondrial inheritance</li> <li>E. Anticipation</li> <li>F. Mutation</li> </ul> <p>Instructions: Match the above types of unusual forms of inheritance with the disorders from the list given below:-</p> <ol style="list-style-type: none"> <li>1. Huntington disease</li> <li>2. Severe osteogenesis imperfecta</li> <li>3. Myoclonic epilepsy with ragged red fibres-MERRF</li> <li>4. Prader Willi and Angelman syndrome</li> <li>5. Beckwith Wiedemann syndrome</li> </ol>	<p><b>Question 102 of 124</b></p> <ul style="list-style-type: none"> <li>A. Breast cancer</li> <li>B. Ovarian cancer</li> <li>C. Familial adenomatous polyposis</li> <li>D. Retinoblastoma</li> <li>E. Lung cancer</li> <li>F. Wilms tumour</li> </ul> <p>Instructions: Match the above cancers with the known causative genes from the choices given below:-</p> <ol style="list-style-type: none"> <li>1. APC gene on Chromosome 5q</li> <li>2. BRCA1&amp;2</li> <li>3. RBI gene on Chromosome 13</li> <li>4. WT gene on Chromosome 11</li> <li>5. Not usually caused by genes</li> </ol>
<p><b>Question 103 of 124</b></p> <ul style="list-style-type: none"> <li>A. Deformation</li> <li>B. Disruption</li> <li>C. Malformation</li> <li>D. Dysplasia</li> <li><del>E. Teratogen</del></li> <li>F. Dystocia</li> </ul> <p>Instructions: Match the above options with the best descriptive statement from the choices given below:-</p> <ol style="list-style-type: none"> <li>1. Chemical agent with a malign influence on development</li> <li>2. Abnormal development of a structure caused by extrinsic forces</li> <li>3. Intrinsic defects in the pattern of development</li> <li>4. Destruction of normally formed tissue</li> <li>5. Abnormal organisation of cells in tissue</li> </ol>	<p><b>Question 104 of 124</b></p> <ul style="list-style-type: none"> <li>A. Single field defects</li> <li>B. Associations</li> <li>C. Sequence</li> <li>D. Developmental field complex</li> <li>E. Synteny</li> <li>F. Syndrome</li> </ul> <p>Instructions: Match the above options with an example from the list given below:-</p> <ol style="list-style-type: none"> <li>1. Hemifacial microsomia</li> <li>2. Down syndrome</li> <li>3. CHARGE</li> <li>4. Potter's syndrome</li> <li>5. Cleft lip</li> </ol>
<p><b>Question 105 of 124</b></p> <ul style="list-style-type: none"> <li>A. Fetal sexing</li> <li>B. Ultrasound scanning</li> <li>C. Chorionic villus sampling</li> <li>D. Amniocentesis</li> <li>E. Maternal serum screening</li> <li>F. Fetal blood sampling</li> </ul> <p>Instructions: Which of the above prenatal diagnostic tests is recommended for the diagnosis of the genetic conditions listed below:-</p> <ol style="list-style-type: none"> <li>1. Cystic fibrosis</li> <li>2. Neural tube defect</li> <li>3. Down syndrome</li> <li>4. To check ambiguous karyotype results obtained at amniocentesis</li> <li>5. X linked disorders with no mutation identified</li> </ol>	<p><b>Question 106 of 124</b></p> <p>A raised maternal serum AFP is associated with the all of the following fetal conditions except:-</p> <ul style="list-style-type: none"> <li>A. Anencephaly</li> <li>B. Cleft palate</li> <li>C. Spina bifida</li> <li><del>D. Exomphalos</del></li> <li>E. Twins</li> </ul>





# **PEDIATRIC ENDOCRINOLOGY**

**By**

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# Pituitary Gland

(The master gland)

## Anterior Pituitary

- Somatotropes → GH (191 aa)
- Lactotropes → Prolactin (199 aa)
- Thyrotropes → TSH (Thyrotropin)
- Corticotropes → ACTH (Corticotropin)
- Gonadotropes → FSH, LH

These hormones are under the control of:

- Hypothalamic neurohormones: via the hypothalamo-hypophyseal portal circulation
- Feedback control

## Posterior Pituitary (Neural hormones)

- ADH (arginine vasopressin)
- Oxytocin

These hormones are **synthesized** in supraoptic & paraventricular nuclei of the hypothalamus and **transmitted** via the axoplasm to be **stored** in the posterior pituitary.

# Growth Hormone

- **Pulsatile** secretion more with sleep
- Action is **mediated** by insulin like growth factor-1 (*IGF-1*) or "somatomedin C" formed by the liver
- **Action:**
  1. **Growth:** ↑↑ Size of various tissues (bones, cartilage, muscles & viscera).
  2. **Proteins:** Anabolic.
  3. **CHO:** ↑↑ Gluconeogenesis.
  4. **Lipids:** ↑↑ Lipolysis.
  5. **Electrolytes:** ↑↑ Ca, ↑↑ Na, ↑↑ PO<sub>4</sub>
- **Control of GH secretion:**

Increase	Decrease
GHRH (GH-releasing hormone)	Somatostatin (also ↓↓ insulin, glucagon, gastrin, VIP)
Synthetic GHRH	Synthetic somatostatin analog ( <i>Octreotide</i> )
Hypoglycemia (Insulin)	Hyperglycemia
↑↑ aa (e.g., arginine)	
Clonidine, L-dopa, Glucagon	
Stress, Sleep, Exercise, Fasting	

# Hypopituitarism

## Definition

It is deficiency of GH with or without other pituitary hormones

## Etiology

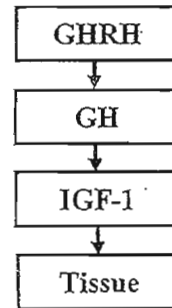
### I) Isolated GH deficiency:

#### A) Genetic

- GHRH receptor gene mutation
- GH gene mutation (AR, AD or X-linked)
- Biologically inactive GH
- GH receptor gene mutation (*Laron syndrome*): Autosomal recessive [↑↑ GH, ↓↓ IGF-1, No response to exogenous GH]
- IGF-1 gene mutation

#### B) Acquired

- Radiotherapy (leukemia)
- Idiopathic



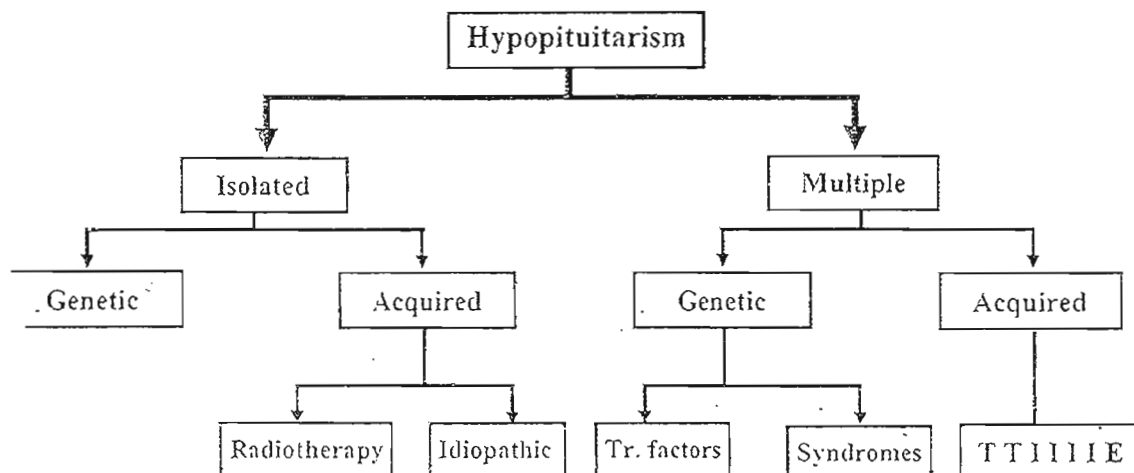
### II) Multiple pituitary hormone deficiency:

#### A) Genetic

- Mutations of transcription factors → Failure of transcription e.g. PROP1, LHX3, LHX4 gene mutation
- Congenital absence of the pituitary gland
- Anencephaly, encephalocele & hydrocephalus
- Septo-optic dysplasia (optic n. dysplasia & maldevelopment of septum pellucidum)
- Holoprosencephaly

#### B) Acquired

- Trauma: birth injury, child abuse, fracture base of skull, surgery
- Tumors: Craniopharyngioma, adenoma, germinoma, optic glioma
- Irradiation (GH deficiency precedes other hormones)
- Infection: meningitis & encephalitis
- Infiltration: histiocytosis X, hemochromatosis, sarcoidosis, TB, Toxoplasmosis
- Immune hypophysitis
- Empty-sella syndrome: congenital or following surgery or irradiation



## Clinical picture

### A) Congenital Hypopituitarism:

#### 1. At Birth:

- Normal weight & height
- Neonatal emergencies: apnea, cyanosis, hypoglycemia, seizures
- Prolonged neonatal jaundice (Conjugated)
- Microphallus in male is an important **diagnostic clue**

#### 2. Infancy & childhood:

- Profound proportionate postnatal growth failure (>2 SD below the mean for age & sex)
- Facies: rounded head, short face, prominent forehead, depressed nasal bridge, small nose, underdeveloped mandible, teeth (Delayed eruption & crowded)
- Intelligence: usually normal
- Sexual maturation: may be delayed
- Hypoglycemia (10%)

### B) Acquired Hypopituitarism:

#### 1. Hormonal manifestations:

- The child is normal initially
- Gradual onset & progressive course of growth failure
- Hypofunction of thyroid, adrenals and gonads
- Diabetes insipidus

#### 2. C/P of the cause:

- Pressure symptoms: ↑↑ ICT, optic atrophy, visual field defects, seizures
- Trauma, infection...

## Investigations

Thyroid hormones are necessary for GH synthesis & action; so must be assessed before GH studies.

### A) Laboratory:

#### 1. GH plasma level

GH level < 10 ng/ mL after 2 provocative tests is diagnostic

- Physiologic stimulation: Sleep (60 min), Exercise (20 min) ??
- Provocative agents: Insulin, clonidine, arginine, glucagon, L-dopa

Measuring GH level every 20 min over (12-24 hr) is used to diagnose *GH neurosecretory dysfunction*.

2. IGF-1: ↓↓ in all cases but ↑↑ with GH administration (except in Laron syndrome)
3. Other pituitary hormones: ACTH, TSH, ADH, Cortisol, T<sub>3</sub>, T<sub>4</sub> (Not FSH & LH)
4. Prolactin: Hyperprolactinemia strongly suggests hypothalamic lesion.
5. TRH stimulation test: ↑↑TSH & prolactin suggests hypothalamic lesion.
6. GHRH stimulation test: ↑↑GH suggests hypothalamic lesion.

### B) Imaging:

- Skull X-ray: beaten silver appearance, separation of sutures, enlargement of sella, destruction of clinoid processes & IC calcification (bone defects in histiocytosis)
- Long bones: delayed bone age:
- CT & MRI

In hypothalamic lesions: ↓↓ all anterior pituitary hormones except prolactin

## Treatment

1. **Treatment of the cause:** Surgery for tumors.
2. **Replacement of pituitary hormones:** Thyroid, hydrocortisone & late sex hormones.
3. **Recombinant human GH (rHuGH)**
  - **Dose:** 0.18-0.3 mg/kg/week, SC in 6-7 divided doses.
  - **Duration:** continuous till closure of epiphyses (NB: leoprolide may be used to delay puberty).

### *Criteria for stopping Rx:*

- Growth rate < 1 inch/year
- Bone age >14 yr in ♀ & >16 yr in ♂

### *- Side effects:*

- Leukemia.
- Hypothyroidism
- Pseudotumor cerebri
- Gynecomastia
- Slipped capital femoral epiphyses, worsening of scoliosis.
- Development of anti-GH antibodies (Rx with IGF-1)

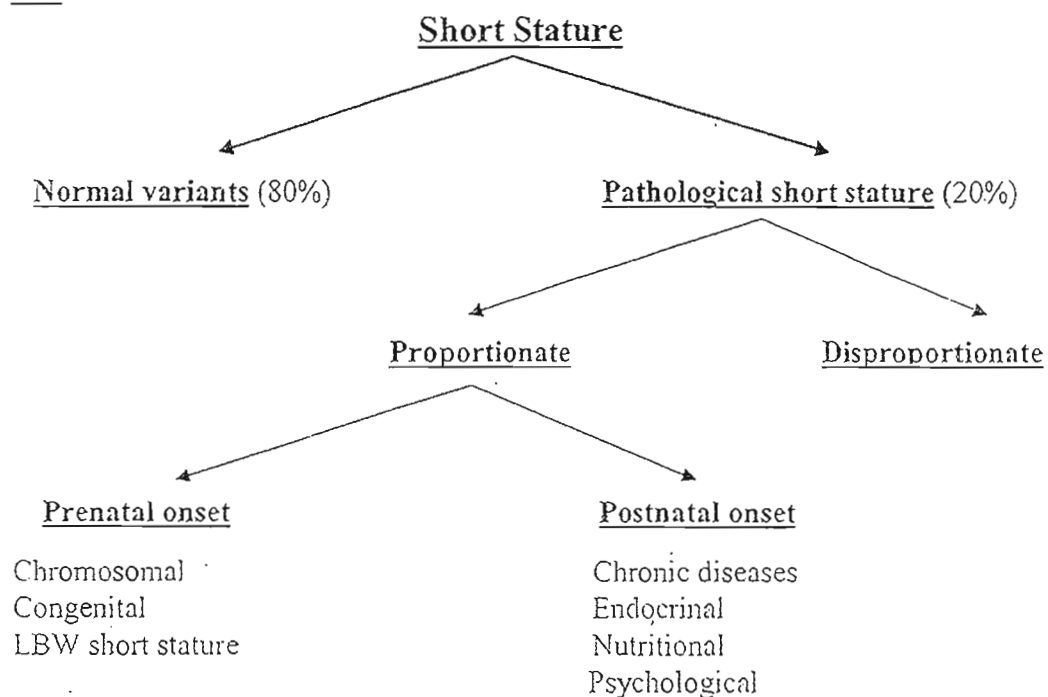
### *- Other indications of hGH:*

- |                    |  |
|--------------------|--|
| • Turner syndrome  | • IUGR   |
| • Noonan syndrome  | • Skeletal dysplasia                                 |
| • ESRD             | • Juvenile rheumatoid arthritis.                     |
| • Prader-Willi \$  | • Familial short stature (some patients may benefit) |
| • Silver-Russel \$ |  |

4. GHRH in hypothalamic causes.

5. Recombinant IGF-1: in Laron \$ & with the development of anti-GH antibodies

DD Short stature.



# Short Stature

## Definition

Height more than 2 SD below the mean height for age & sex or < 5<sup>th</sup> percentile.

**Pathologic short stature:** Height >3 SD below the mean height for age & sex.

## Nomenclatures

**Lower segment:** Measured from the upper border of the symphysis pubis to the floor.

**Upper segment:** Total height – lower segment.

**Arm span:** Distance between the tips of middle fingers when the arms are fully extended.

**Supine length:** (birth to 2-3 yrs). The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard. The head should be in the "Frankfurt plane" (ear hole to lower border of eye socket).

**Standing height:** measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane".

## U/L ratio:

- At birth: 1.7 (Umbilicus is in the middle)
- At 3 yrs: 1.3
- At 7 yrs: 1 (Symphysis is in the middle)

## Arm span -- height:

- 1<sup>st</sup> 7 yrs: -3
- 8-12 yrs: Zero

## Classification

### A) Proportionate or Disproportionate

1. Proportionate short stature: normal values are obtained
2. Disproportionate short stature: abnormal values are obtained

### B) Type of short stature

1. Short limbs
2. Short trunk

Ratio	Short Limbs	Short Trunk
U/L	High	Low
Arm span/Height	Low	High

### C) Classification of short limbs

1. Rizomelic: proximal shortening of humerus & femur (e.g., achondroplasia)
2. Mesomelic: middle segment shortening of radius & ulna, tibia & fibula.
3. Acromelic: terminal shortening of fingers.

## MPH & TCR

Mean parental height = (Father's height + Mother's height) / 2

Mid Parental Height (MPH) for ♂ = Mean parental height + 7

Mid Parental Height (MPH) for ♀ = Mean parental height - 7

Target Centile Range (TCR) for ♂ = MPH ± 12

Target Centile Range (TCR) for ♀ = MPH ± 11

## Etiology

### A) Normal variants (80%)

	1. Familial (genetic)	2. Constitutional growth delay
Family history	Positive (parents are short)	Positive
Growth velocity	Normal	Period of transient decelerated growth
Bone age	Normal	Delayed
Puberty	Normal	Delayed
Adult height	Short adult height	Normal adult height
Treatment	GH may be useful	Reassurance

### B) Pathological (20%)

#### 1. Endocrinal

- Hypothalamus: Laurant-Moon Biedl
- Pituitary: Hypopituitarism
- Thyroid: Congenital hypothyroidism
- Suprarenal: Cushing, CAH
- Gonads: Precocious puberty
- Pancreas: DM

#### 2. Chronic debilitating diseases

- CVS: CHD, RHD
- Resp.: TB, Cystic fibrosis, asthma
- Renal: CRF, RTA, DI
- GIT: Malabsorption, IBD
- Immunodeficiency
- Hepatic: Cirrhosis, Wilson's
- Collagen: JRA
- Blood: Chronic hemolytic anemia
- Infection: TB, suppurative lung S.
- Metabolic: aa, organic acidemias

#### 3. Chromosomal

- Turner
- Down
- Trisomy 18

#### 4. Congenital syndromes

- Prader-Willi
- Silver-Russell
- Cornelia De Lange (microcephaly, synophrys...)
- Progeria

#### 5. Metabolic

- Aminoacidopathies
- Organic acidemias
- Storage diseases (Gaucher, NP...)
- Minerals: Cu, Fe...

#### 6. Psychological (deprivation) dwarfism

- Disturbed child-mother or family relation → ↓↓ GH release (Unknown mechanism)
- Growth will be resumed if the child is provided with love & care (i.e., Catch-up)
- Bone age is delayed

#### 7. Malnutrition: Malnutrition → ↓↓ Synthesis of GH mediators (Growth factors)

#### 8. Skeletal (=Causes of Disproportionate short stature)

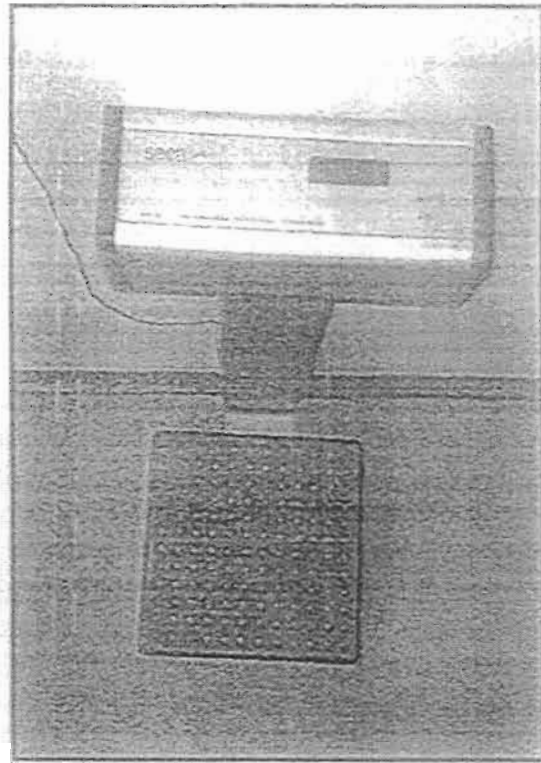
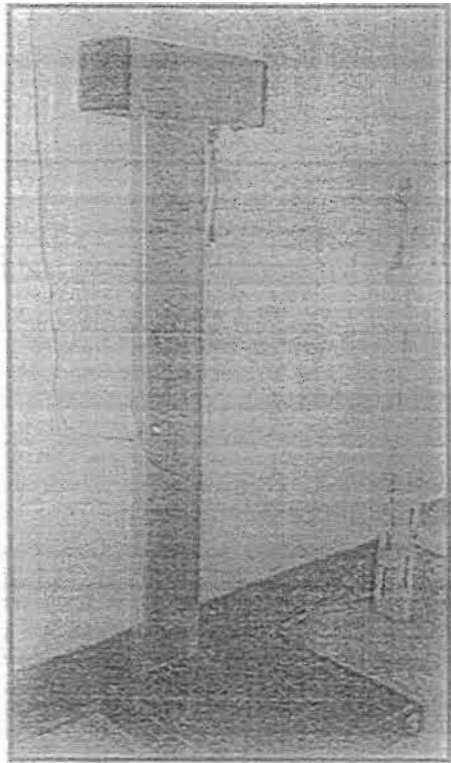
- Rickets
- Achondroplasia (large head, short limbs & normal trunk) + Normal mentality
- Hypochondroplasia (normal head + Features are not prominent as achondroplasia)
- Osteogenesis imperfecta (osteoporosis + multiple fractures + blue sclera + hearing ↓↓)
- Mucopolysaccharidoses
- Chondroectodermal dysplasia (short limbs + ectodermal dysplasia + polydactyly + CHD)

#### 9. Primordial short stature (LBW short stature)

- IUGR (Congenital infections, Congenital malformation, placental insufficiency)
- Silver-Russell syndrome (triangular face, incurved 5th finger, hemihypertrophy)
- Seckel syndrome (Bird-headed dwarfism)

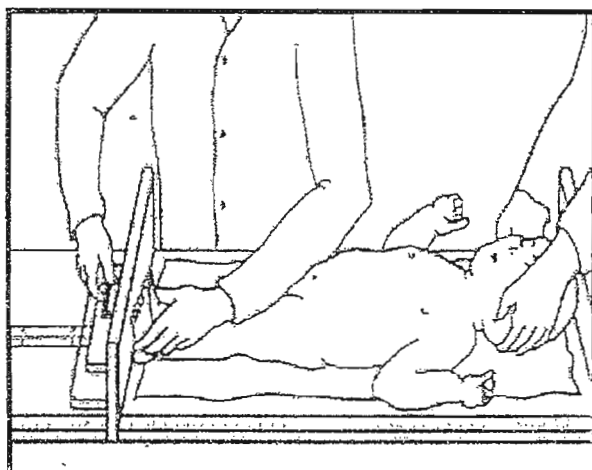
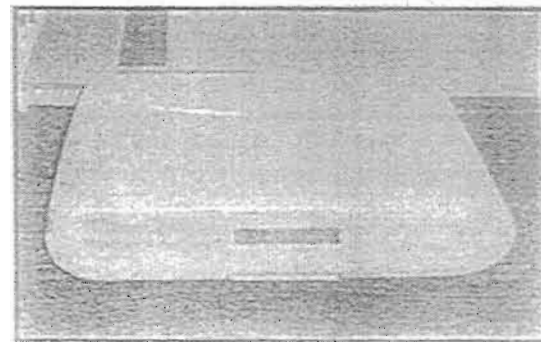
#### 10. Drugs: Steroids

## Instruments for Weight & Height Measurement

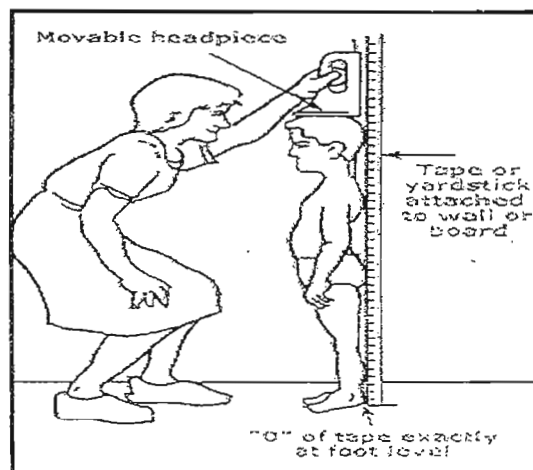


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer  
Height is measured using stadiometer



# Diabetes Insipidus

(Insipidus = Tasteless)

## Physiology of ADH (ADH = arginine vasopressin)

### ☒ Control of ADH secretion:

- Plasma osmolality:  $\uparrow\uparrow$  Osmolality  $\rightarrow$   $\uparrow\uparrow$  Osmoreceptors  $\rightarrow$   $\uparrow\uparrow$  ADH release
- Extracellular volume:  $\downarrow\downarrow$  ECV  $\rightarrow$   $\uparrow\uparrow$  Baroreceptors  $\rightarrow$   $\uparrow\uparrow$  ADH release
- Stress, pain, drugs (nicotine).

### ☒ Action of ADH:

- ADH binds to vasopressin type-2 receptors ( $V_2 R$ ) in the collecting ducts  $\rightarrow$   $\uparrow\uparrow$  cAMP
- $\rightarrow$  movement of preformed aquaporin water channels ( $AQP-2$ ) to apical membrane
- $\rightarrow$   $\uparrow\uparrow$  water permeability  $\rightarrow$   $\uparrow\uparrow$  water movement to the *hypertonic* medullary interstitium
- $\rightarrow$   $\uparrow\uparrow$  water reabsorption

## Definition

Inability to produce concentrated urine due to:

- Defect in ADH *secretion*  $\rightarrow$  Central DI
- Defect in ADH *action*  $\rightarrow$  Nephrogenic DI

## Etiology

Central DI	Nephrogenic DI
<b>A) Hereditary:</b> AD mutation of ADH gene	<b>A) Hereditary:</b> -XLR mutation of $V_2R$ gene* -AR/AD mutation of $AQP-2$ gene
<b>B) Acquired:</b> <ul style="list-style-type: none"> <li>• Trauma</li> <li>• Tumors</li> <li>• Irradiation</li> <li>• Infection</li> <li>• Infiltration</li> <li>• Immune</li> <li>• Empty-sella syndrome</li> </ul>	<b>B) Acquired:</b> <ul style="list-style-type: none"> <li>• Obstructive uropathy</li> <li>• Interstitial nephritis</li> <li>• VUR</li> <li>• Chronic pyelonephritis</li> <li>• Sickle cell anemia</li> <li>• CRF</li> <li>• Cystic diseases</li> <li>• Nephrocalcinosis</li> <li>• Hypokalemia</li> <li>• Hypercalcemia</li> </ul>
<b>C) Drugs:</b> Alcohol	<b>C) Drugs:</b> Amphotericin B Lithium Demeclocyclin
<b>D) Idiopathic:</b> (diagnosis of exclusion) Periodic F/U is required for at least 4 yrs as DI may precede brain tumors	
<b>E) DIDMOAD (Wolfram Syndrome):</b> DI, DM, Optic Atrophy & Deafness	

## Serum Osmolality

- Serum osmolality =  $2Na + \text{Glucose}/18 + \text{BUN}/3$
- Normally = 285-295 mOsm/Kg

Osmolality =  $2Na + \text{Glucose}/18 + \text{BUN}/3$

## Clinical picture

- Polyuria ( $>2 \text{ L/m}^2/\text{day}$ ) & polydipsia, satisfied with water not by milk.  
(NB: Breast milk has a low Na content; infants receiving cow's milk are more liable to hypernatremic dehydration).
- Dehydration, bouts of high fever.
- FTT
- Irritability & seizures ( $\uparrow\uparrow \text{ Na}$  & its correction).
- Nocturia & Enuresis.
- Picture of the cause in acquired forms of central & nephrogenic DI.

## Investigations

Diagnosis of DI is established if serum osmolality  $>300 \text{ mOsmol/Kg H}_2\text{O}$  and urine osmolality  $<300 \text{ mOsmol/Kg H}_2\text{O}$

Diagnosis of DI is unlikely if serum osmolality  $<270 \text{ mOsmol/Kg H}_2\text{O}$  or urine osmolality  $>600 \text{ mOsmol/Kg H}_2\text{O}$

### 1. Urine:

- Volume: Polyuria up to 4-10 L/day
- Specific gravity: Low  $<1010$
- Osmolality: Low  $<300 \text{ mOsmol/Kg H}_2\text{O}$

### 2. Blood:

- Na: Normal or  $\uparrow\uparrow$
- Osmolality: Normal or  $\uparrow\uparrow >300 \text{ mOsmol/Kg H}_2\text{O}$

### 3. Vasopressin test: To differentiate between central & nephrogenic DI using intranasal Desmopressin (DDAVP=Desamino-D-arginine vasopressin= Minirin)

- $\uparrow\uparrow$  Urine osmolality (Central DI)
- No  $\uparrow\uparrow$  urine osmolality (Nephrogenic DI)

### 4. Water deprivation test: "If serum osmolality is 270-300 mOsmol/Kg".

Fluids are withheld (3-5 hr) with periodic measurement of urine & blood osmolality, and then vasopressin is given as before. [Stop if BW  $\downarrow\downarrow >3\%$ ]

### 5. Vasopressin plasma level: Low in central DI.

### 6. Investigation of the cause: $\downarrow\downarrow \text{ K}$ , $\uparrow\uparrow \text{ Ca}$ , KFTs, MRI brain.

### 7. Renal US: Hydronephrosis & Hydronephrosis "functional" (2 ry to persistent polyuria).

## Treatment

1. Adequate fluid intake: free access to water.
2. Adequate caloric intake & low Na content: Breast milk & low Na formula.
3. Rx of the cause.

Central DI	Nephrogenic DI
<b>Desmopressin</b> (DDAVP=Desamino-D-arginine vasopressin= Minirin) Nature: synthetic analogue of ADH Dose: $10 \mu\text{g}$ intranasal qd. (IV, tablets) Other uses: Nocturnal enuresis Hemophilia A vWD Donors of cryoprecipitate Platelet dysfunction Portal hypertension Renal/liver biopsy	<b>1. Diuretic therapy</b> <ul style="list-style-type: none"> <li>• Hydrochlorothiazide: 2-4 mg/kg/day</li> <li>• Amiloride: 0.3 mg/kg/day</li> </ul> Mechanism: "paradoxical response" $\downarrow\downarrow \text{ Na} \rightarrow \uparrow\uparrow \text{ PCT Na reabsorption} \rightarrow$ $\downarrow\downarrow \text{ H}_2\text{O delivery to defective DCT}$
	<b>2. Indomethacin therapy</b> (PGs inhibitor) Dose: 2 mg/kg/day Mechanism: PGs $\rightarrow \downarrow\downarrow \text{ cAMP}$ Side effects: GIT, renal impairment

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# Syndrome of Inappropriate ADH Secretion

## Definition

Inappropriately high plasma level of ADH not inhibited by ↓↓ serum osmolality or ↑↑ intravascular volume.

## Etiology

1. **Overtreatment of central DI\***
2. **CNS:** Encephalitis, TB meningitis, brain abscess, brain tumors, head trauma, surgery, postictal period, Guillain-Barre syndrome
3. **Respiratory:** Pneumonia, cystic fibrosis, +Ve pressure ventilation, pneumothorax
4. **Tumors:** Thymus, lung, Ewing's sarcoma
5. **Drugs:** vincristine & carbamazepine

## Clinical picture

1. **Picture of the cause**
2. **Plasma volume:** Normal or slightly ↑↑
3. **Asymptomatic:** If serum Na > 120mEq/L
4. **Water intoxication:** Anorexia, nausea, vomiting, confusion, seizures.

## Investigations

1. **Hyponatremia** (<135 mEq/L), hypochloremia & *hypouricemia*
2. Plasma osmolality < 280 mOsmol/Kg H<sub>2</sub>O
3. Urine osmolality > 100 mOsmol/Kg H<sub>2</sub>O (usually > plasma osmolality)
4. Urine specific gravity ↑↑
5. Urine Na > 25mEq/L

## Treatment

1. Fluid restriction (1L/m<sup>2</sup>/d)
2. Frusemide with Na supplementation
3. Hemodialysis → Removal of excess water & normalization of electrolytes
4. Demeclocyclin (creation of nephrogenic DI)

	Homocystinuria	Marfan syndrome
<b>Etiology</b>	Cystathionine synthase ↓↓	Defect in collagen fibers
<b>Inheritance</b>	AR	AD
<b>Mentality</b>	MR	Normal
<b>Muculoskeletal</b>	Arachnodactyly (2 Tests), Pectus excavatum, High arched palate, Kyphoscoliosis	The same + Hernias Pneumothorax
<b>Bone density</b>	Osteoporosis	Normal
<b>Joints</b>	Stiff	Lax
<b>Cardiovascular</b>	AR, MR	AR, MR, Aortic dissection
<b>Ocular</b>	Myopia Lens dislocation (Downwards).	Myopia Lens dislocation (Upwards)
<b>Vascular thrombosis</b>	↑↑ risk of thrombosis	No ↑↑ risk of thrombosis
<b>Investigations</b>	↑↑ Homocystine in urine	No ↑↑ Homocystine in urine
<b>Treatment</b>	Low methionine diet B6 & folic acid	Supportive

# Puberty

## Definition

It is the period of life during which the **endocrine** & **gametogenic** functions of the gonads have developed to the point where reproduction is possible [physical & sexual maturation]

## Adolescence

It is the period of life during which child becomes an adult [Physical, sexual, psychological & social maturation]. So, puberty is 1<sup>st</sup> part of adolescence.

## Physiology of Puberty

Sex hormones = Testosterone & Estrogen

- Prepubertal stage:
  - Hypothalamo-hypophyseal-gonadal axis is dormant (upper neuronal inhibition)
  - ↑↑ Sensitivity of H-H-G axis to sex hormones
  - LH & sex hormones: undetectable
- 1-3 yrs before puberty:
  - GnRH & LH pulsatile secretion start to occur first during sleep
  - Gradual ↑↑ in amplitude & frequency of GnRH & LH pulses
  - Adrenarche: ↑↑ adrenal androgens (responsible for pubic hair, acne, voice...)
- During puberty:
  - GnRH & LH pulsatile secretion occur at 90-120 min intervals
  - No more diurnal variation
  - In ♀, +Ve feedback effect of estrogen causing LH surge in midcycle (ovulation)

## Age of Onset of Puberty (Variable)

♀ = 8-13 yrs      ♂ = 9-14 yrs

## Factors affecting the age of Onset of Puberty

1. Osseous maturation (bone age):
  - The onset of puberty is more closely related to osseous maturation than to chronological age
  - Estrogen is responsible for bone maturation & epiphyseal closure in both ♀ & ♂
2. Genetic factors
3. Nutrition: Good nutrition → earlier puberty
4. Body build: Moderate obesity → earlier puberty, Morbid obesity → delayed puberty
5. Physical activity (energy balance): ♀ athletes (ballet dancers & swimmers) → delayed puberty

## Physical changes of Puberty

### ☒ Females:

- First sign of puberty is breast enlargement
- Followed by → Pubic hair → Axillary hair → Menarche
- Average age of menarche in Egyptian ♀ is 12.5 yrs
- Less obvious changes: ↑↑ Ovaries, uterus, labia & thickening of vaginal mucosa

### ☒ Males:

- First sign of puberty is testicular enlargement (Prader orchidometer)
- Followed by → Thinning & pigmentation of the scrotum → ↑↑ Penis → Pubic hair → Axillary hair
- Less obvious changes: ↑↑ epididymis, seminal vesicles, prostate & gynecomastia (65%)

- Prader orchidometer (12-ellipsoids): 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25 ml
- Testicular volume: Preadolescence = 1-3 ml
- Testicular length (exclude epididymis): Preadolescence = 1.5-3 cm

## Stages of Puberty (=Tanner staging)

### ☒ Females:

Stage	1. Pubic Hair	2. Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

### 3. Axillary hair (3 stages)

- No
- Appearance
- Adult type

### ☒ Males:

Stage	1. Pubic Hair	2. Penis	3. Testes
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, at the base of the penis	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth )	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

### 4. Axillary hair (as in females)

## Secondary Sex Characters

2ry Sex Ch.	Male	Female
Voice	Deep	High pitched
Hair distribution	Beard, frontal baldness, chest, pubic hair (triangle with apex up)	Less body hair, ↑↑ scalp hair, pubic hair (triangle with base up)
Body shape	Masculine	Fat distribution (breast & buttocks)
skeleton	Wide shoulders, Narrow hips	Narrow shoulders, wide hips
Libido	↑↑ Libido	↑↑ Libido

## Growth

- **Definition:** Increase in the **size & number** of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Fetal: Fastest period of growth (*See factors affecting IU growth*)
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone (& Thyroxine)
  - Puberty: Sex hormones (& Growth hormone)

## Pubertal growth spurt

It is divided into 3 phases:

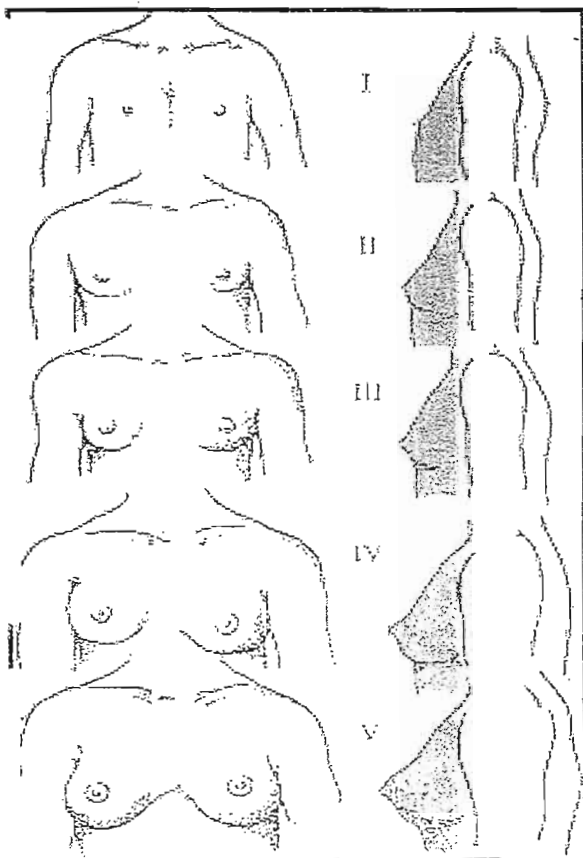
- Take-off = Minimum growth velocity
- Peak height velocity = Maximum growth velocity
- Decelerated phase

### ☒ Females:

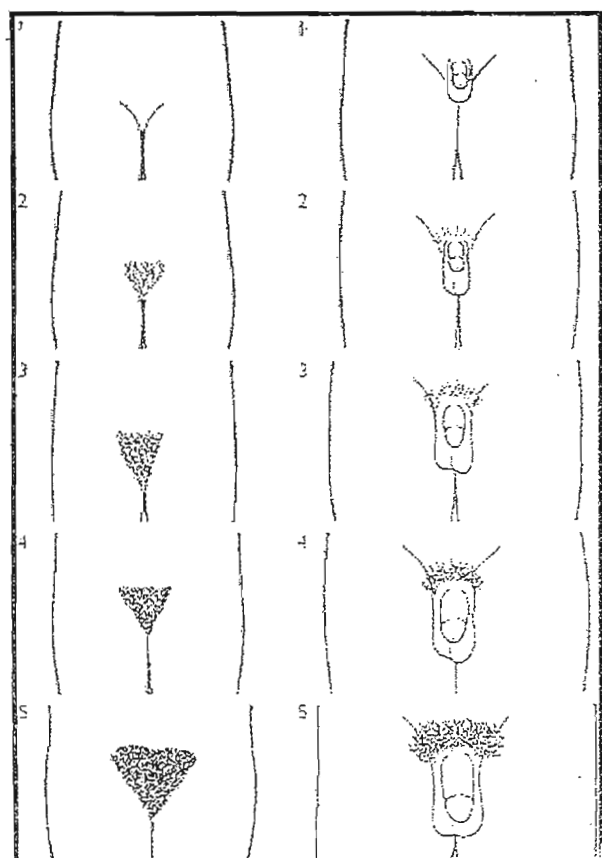
- Onset of peak height velocity = pubertal stage 2-3 [i.e., pre-menarcheal event]
- Height gain = 25 cm

### ☒ Males:

- Onset of peak height velocity = pubertal stage 3-4 [2 yrs after females]
- Height gain = 28 cm [Mean height difference between ♂ & ♀ = 13 cm, why??]



Tanner staging of female breast changes



Tanner staging of pubic hair

# Glucose Homeostasis

## Sources of blood glucose

1. Dietary carbohydrates (glucose, galactose, fructose)
2. Glycogenolysis (liver): Breakdown of glycogen into glucose or G-6-P
3. Gluconeogenesis: Synthesis of glucose from non-CHO sources  
(Lactate, pyruvate, proteins, glycerol, FA)

## Removal of glucose from the blood

1. Tissue uptake: Glucose transporter (GLUT); may be insulin dependent (muscles & fat) or insulin independent (liver,  $\beta$ -cells, RBCs, brain)
  2. Oxidation: mainly glycolysis followed by Krebs' cycle
  3. Glycogenesis: Synthesis of glycogen from glucose
  4. Lipogenesis: Synthesis of triacylglycerols (TAG) from CHO
- "Glucose Utilization"

## Organs regulating blood glucose

1. GIT: prevents excessive hyperglycemia after a CHO meal
2. Liver: most important "glucostat"
3. Muscle & adipose tissue
4. Kidneys: prevent glucose loss "Renal threshold = 180 mg/dL"

## Hormones regulating blood glucose

1. Insulin: The only hypoglycemic hormone ( $\uparrow\uparrow$  uptake & utilization,  $\downarrow\downarrow$  production)
  2. Adrenaline & glucagon
  3. Glucocorticoids
  4. GH
  5.  $T_3$  &  $T_4$
- Anti-insulin hormones

## Overall regulation

1. CHO meal  $\rightarrow \uparrow\uparrow$  blood glucose  $\rightarrow \uparrow\uparrow$  insulin  $\rightarrow \uparrow\uparrow$  uptake & utilization
2. Fasting  $\rightarrow \downarrow\downarrow$  blood glucose  $\rightarrow \downarrow\downarrow$  insulin &  $\uparrow\uparrow$  anti-insulin  $\rightarrow \downarrow\downarrow$  uptake & utilization and  $\uparrow\uparrow$  production ( $\uparrow\uparrow$  glycogenolysis,  $\uparrow\uparrow$  gluconeogenesis)

## Normal blood glucose

- Normally = 60-100 mg/dL (3.5-5.5 mmol/L). Serum is > whole blood readings, why?
- Fluorides are added to blood samples to  $\#$  glycolysis which  $\downarrow\downarrow$  Blood glucose

## Insulin

- It is a peptide hormone (51 aa), synthesized in the  $\beta$ -cells of the islets of Langerhans
- Proinsulin (= A chain + B chain + Connecting peptide "C-peptide")  $\rightarrow$  Insulin
- The C peptide is secreted along with insulin (Index of the rate of insulin secretion)

### Action:

- o CHO  $\rightarrow \uparrow\uparrow$  Uptake & utilization,  $\downarrow\downarrow$  glycogenolysis,  $\downarrow\downarrow$  gluconeogenesis
- o Fats  $\rightarrow \uparrow\uparrow$  Lipogenesis,  $\downarrow\downarrow$  lipolysis (breakdown of TAG into FA)  
 $\downarrow\downarrow$  ketogenesis (formation of ketone bodies)  
 $\uparrow\uparrow$  ketolysis (oxidation of ketone bodies into  $CO_2$  &  $H_2O$ )
- o Ptn  $\rightarrow$  Anabolic
- o Potassium  $\rightarrow$  Intracellular shift  $\rightarrow \downarrow\downarrow K^+$

### Control of secretion:

- o Stimulators: glucose, amino acids (e.g., arginine..), glucagons, ketone bodies, drugs (sulphonylurea)
- o Inhibitors: hypoglycemia, somatostatin, drugs (diazoxide)

Syndrome X (Metabolic syndrome)  
= Insulin resistance syndrome  
Insulin resistance, Hyperinsulinemia,  
Obesity, Dyslipidemia & HTN



# Solitary Thyroid Nodule

## Etiology

1. Simple nodular goiter (with one palpable nodule)
2. Lymphocytic thyroiditis (with one prominent lymphoid follicle)
3. Toxic nodule
4. Inflammatory nodule (Abscess)
5. Developmental
  - Thyroglossal cyst
  - Agénesis of one lobe (hyperplasia of the other)
6. Neoplastic
  - Beign: Adenoma, teratoma
  - Malignant:
    - Follicular epithelium: Papillary, follicular& anaplastic
    - Parafoallicular (C- cells): Medullary carcinoma

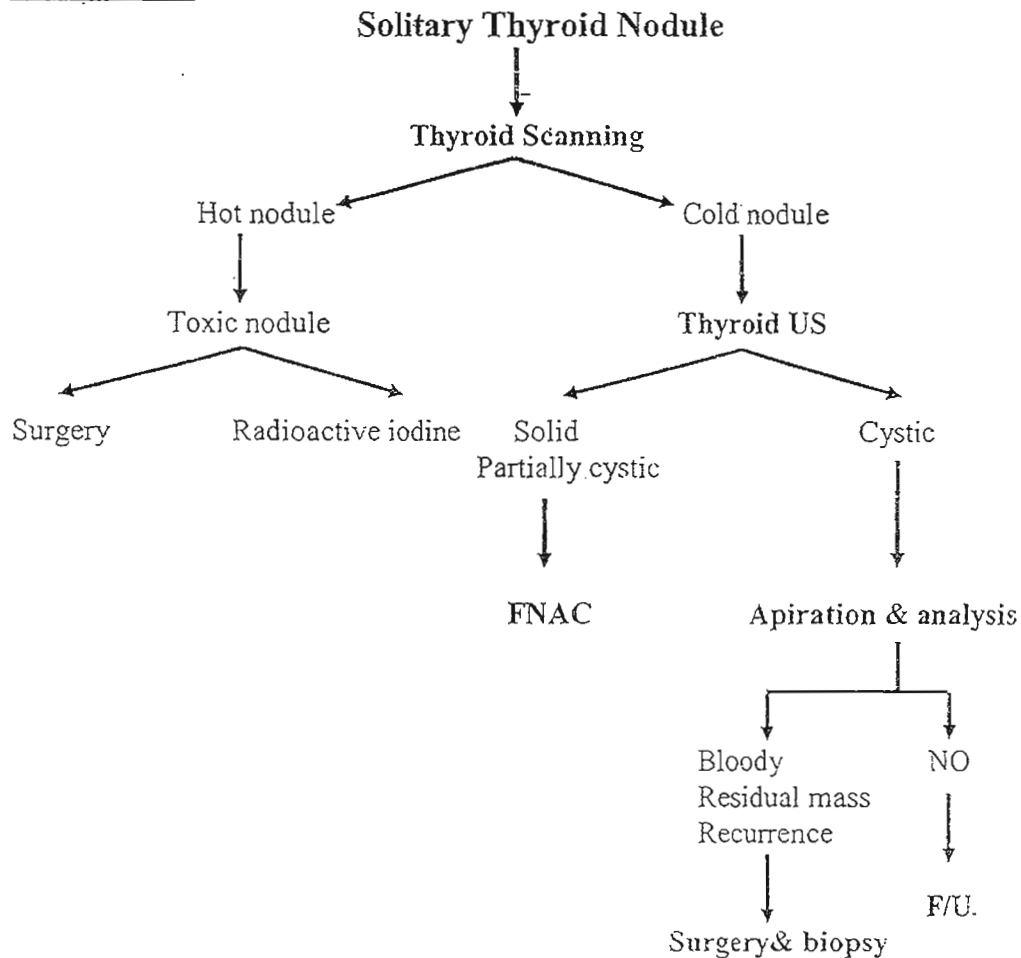
## Diagnostic approach:

### Clinical evaluation

- History
- Examination:

Most hot nodules are benign

### Investigations



# Tall Stature

## Definition

Height more than 2 SD above the mean height for age & sex or > 97<sup>th</sup> percentile.

## Etiology

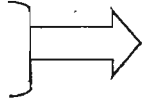
### 1. Familial (genetic or constitutional)

- +Ve family history.
- Normal bone age
- Normal puberty
- Tall adult height.

### 2. Exogenous obesity

### 3. Precocious puberty

### 4. Hyperthyroidism



-Advanced bone age

-Tall child height

-Normal adult height

### 5. Marfan: ↑↑ arm span, ↓↓ US/LS

### 6. Homocystinuria:

### 7. Klinefelter (XXY) & XYY syndrome

### 8. McCune-Albright syndrome

### 9. Cerebral gigantism (Sotos syndrome):

- Growth rate: -At birth → Macrosomic -1-5 yrs: accelerated rate of growth
- >5 yrs → Normal growth rate - Normal adult height
- Physical: Large head, dolicocephaly, hypertelorism, prominent jaw, large hands & feet
- Mental: MR
- Sexual: Normal
- ↑↑ Risk of malignancy (Wilms, liver)
- Normal endocrinal studies.

### 10. GH excess → Open epiphyses → Gigantism

→ Closed epiphyses → Acromegaly

(Skull, coarse facies hands, feet, jaw, tongue, kyphosis, IGT)

## Etiology:

- ☒ Hyperplasia
- ☒ Adenoma (GH-secreting)

## Investigations:

- ↑↑ GH (No ↓↓ with hyperglycemia)
- ↑↑ IGF-I
- ↑↑ Prolactin (in case of pituitary adenoma secreting both GH & prolactin)
- ↓↓ Pituitary hormones (compression by adenoma)
- Skull X-ray, CT & MRI brain

## Treatment:

- Surgical removal of adenoma
- Irradiation (hypopituitarism)
- Somatostatin analogues (*Octreotide*)
- Bromocriptine (dopamine agonist) in cases with ↑↑ prolactin
- GH receptors antagonist (*Pegvisomant*)

Dopamine = Prolactin-inhibiting factor

## Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann S
3. Cerebral gigantism (Sotos)
4. IGF-II excess

## Treatment of familial tall stature

♂ → Testosterone enanthate

♀ → Ethinyl estradiol

When: Predicted adult height > 3 SD

Severe psychological impairment

## Approach to a case of short stature

### (A) History:

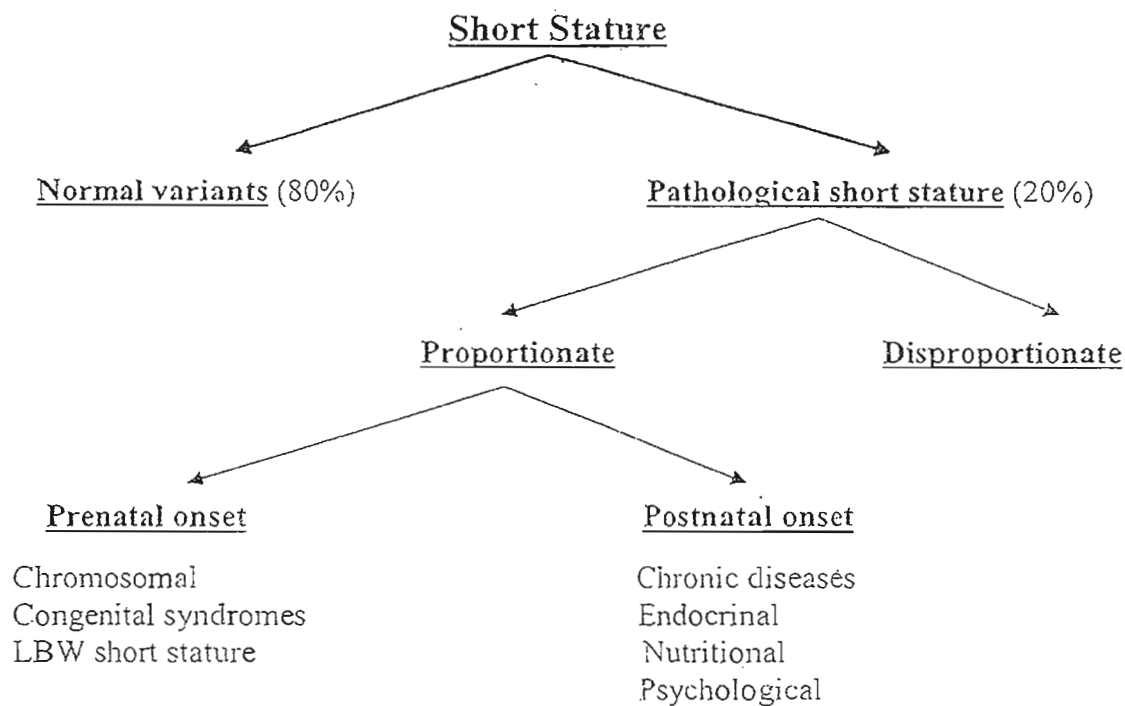
- Symptoms of different system affection
- Nutritional history
- Perinatal history: Birth length & weight, causes of IUGR
- Psychological assessment
- Parental heights & TCR

### (B) Physical examination:

- Measure height/length, US & LS, arm span → Proportionate or disproportionate
- Manifestations of chromosomal abnormalities (e.g., Turner...), congenital syndromes (e.g., Prader-Willi), hypopituitarism (microphallus)
- Complete system examination.

### (C) Investigations:

- CBC, ESR, UA, electrolytes, KFTs, LFTs
- Karyotyping is routine in all ♀ with short stature
- Bone age (Lt wrist X-ray): normal in familial cases & skeletal dysplasia
- Imaging: CT, MRI
- Investigations of endocrinal causes (start with thyroid): *See before*



# Goiter

## Definition

It is thyroid enlargement (whatever the etiology). It may be associated with euthyroidism, hypothyroidism or hyperthyroidism. It may be congenital or acquired

## Etiology

1. **Simple** (Non-toxic, non-neoplastic, non-inflammatory thyroid enlargement)
  - Physiological: usually occurs in pubertal ♀ due to relative iodine deficiency  
→ (*Venus neck*). Rx: Reassurance, L-thyroxine may be indicated
  - Simple nodular goiter: repeated cycles of stress & fluctuation of TSH levels
  - Colloid goiter: intermediate stage
2. **Toxic goiter**
  - Graves (Diffuse toxic goiter)
  - Plummer disease (Nodular toxic goiter)
  - Toxic nodule (autonomous function with suppression of the rest of the gland – hot nodule on scanning)
3. **Inflammatory**
  - Lymphocytic thyroiditis
  - Acute suppurative thyroiditis
  - Subacute non suppurative thyroiditis
  - Chronic thyroiditis
4. **Iodide goiter**  
Long term administration of iodides → ↓↓ organification → ↑↑ TSH → goiter  
E.g., Amiodarone (1/3 weight = iodine) → hypothyroidism & goiter
5. **Neoplastic**
  - Benign: Adenoma, teratoma
  - Malignant:
    - Follicular epithelium: Papillary, follicular & anaplastic
    - Para-follicular (C-cells): Medullary carcinoma
      - ☑ Sporadic
      - ☑ Familial (AD): Multiple endocrine neoplasia (MEN)
    - ❖ MEN type I: Parathyroid, Pancreas, Pituitary
    - ❖ MEN type IIA: Medullary carcinoma, Pheochromocytoma, Parathyroid
    - ❖ MEN type IIB: Medullary carcinoma, Pheochromocytoma, neuromas of mucous membranes (lips, tongue...)
6. **Developmental**
  - Thyroglossal cyst
  - Agenesis of one lobe (hyperplasia of the other)
7. **Congenital goiter** (may cause RD)
  - Defective hormone synthesis\* (dyshormonogenesis)
  - Iodine deficiency\* (maternal) & Iodine exposure\*
  - Maternal medications (Amiodarone, methimazole, propylthiouracil)\*
  - Thyroid hormone unresponsiveness\*
  - Teratoma
  - Transient neonatal thyrotoxicosis (Congenital hyperthyroidism):
    - Type of the mother: Graves (active/ remission) or lymphocytic thyroiditis
    - Mechanism: Transplacental passage of TRSAb
    - C/P: Goiter, IUGR, irritability, exophthalmos, ↑↑ HR, HF, RD, hyperthermia
    - Treatment: IVF, propranolol, PTU ± Lugol's iodine ± digitalis
    - Prognosis: Transient. Most cases remit within 3-4 months

### C) Ophthalmopathy:

- Pain, photophobia, blurring of vision, bulging
- Exposure keratitis
- Periorbital edema
- Exophthalmos
- *Stellwag's sign*: staring look with infrequent blinking
- *Mobius' sign*: defective convergence (muscle weakness)
- *Von Graefe's sign*: lid lag when looking downwards
- *Dalrymple's sign*: appearance of a rim of sclera above the cornea

#### DD of Graves disease:

1. Hyperthyroidism
2. Thyroid hormone unresponsiveness

D) Thyrotoxic crisis (follows thyroid surgical manipulation, trauma or infection)  
Hyperpyrexia, excessive sweating, tachycardia, arrhythmia, coma, convulsions

### Investigations

- Thyroid functions ( $\uparrow\uparrow T_4$  &  $T_3$ ,  $\downarrow\downarrow$  TSH,  $\uparrow\uparrow$  Thyroglobulin)
- Thyroid autoantibodies...
- Radioactive iodine uptake  $\uparrow\uparrow$

### Treatment

#### A) Medical treatment:

1. Sedatives:
2.  $\beta$ -adrenergic blockers: Propranolol<sup>†</sup>  $\rightarrow$  # Catecholamine action (Cardioprotector)  
Dose: 0.5-2 mg / day divided every 8 hrs
3. Anti-thyroid drugs (Methimazole, Propylthiouracil)
  - o Action: # Organification  
 $\downarrow\downarrow$  TRSAb  
PTU  $\rightarrow$  inhibits peripheral conversion of  $T_4$  to  $T_3$
  - o PTU has lesser ability to cross the placenta & to pass in breast milk
  - o Dose: Methimazole = 0.5-1 mg / day single daily dose  
PTU = 5-10 mg / day divided every 8 hrs
  - o Side effects:
    - Allergy (rash) & Agranulocytosis (monitor with CBC)
    - $\uparrow\uparrow$  TSH,  $\uparrow\uparrow$  size & vascularity of thyroid
    - $\uparrow\uparrow$  Exophthalmos
    - Liver, kidney, GIT

#### B) Subtotal thyroidectomy:

- o Indication: Failure of medical treatment
- o Preoperative preparation: Methimazole or PTU  $\rightarrow$  Euthyroid state (2-3 months)  
Lugol's iodine  $\rightarrow \downarrow\downarrow$  Size & vascularity (in the last 2 wks)
- o Complications:
  - Hypothyroidism
  - Hypoparathyroidism
  - Vocal cord paralysis (recurrent laryngeal nerve injury)
  - Thyrotoxic crisis

#### C) Radioactive iodine ( $I^{131}$ ): in children >10 yrs

Complications: Hypothyroidism, adenoma formation

#### D) Treatment of ophthalmopathy: Prednisone or radiotherapy

#### E) Treatment of Thyrotoxic crisis: Propranolol, Temperature control, PTU, Iodide, Hydrocortisone, IVF, Rx of precipitating factor (infection)

# Hyperthyroidism

## Definition

Excessive secretion of thyroid hormones

## Etiology

1. Graves disease (Diffuse toxic goiter)
2. Toxic nodular goiter (Plummer disease)
3. Lymphocytic thyroiditis "Hashitoxicosis"
4. Acute & subacute non-suppurative thyroiditis (De Quervain disease)
5. TSH secreting pituitary tumor
6. Activation mutation of TSH receptor
7. McCune Albright syndrome
8. Hyperfunctioning thyroid adenoma or carcinoma
9. Transient neonatal thyrotoxicosis (Infants born to mothers with Graves disease)
10. Thyrotoxicosis factitia ( $\uparrow\uparrow T_4$ ,  $\downarrow\downarrow$  TSH & very low thyroglobulin level)

# Graves Disease

## Definition

It is the commonest cause of hyperthyroidism

## Etiology

Autoimmune

## Pathogenesis (= Evidence of immune nature)

1. Lymphocytic infiltration of the thyroid (T & B cells)
2. Thyroid autoantibodies
  - Thyrotropin receptor stimulating antibodies (TRSAbs)  $\rightarrow \uparrow\uparrow$  TSH receptors
  - Thyrotropin receptor blocking antibodies (TRBAbs)
  - Exophthalmogenic immunoglobulin (EI)  $\rightarrow \uparrow\uparrow$  GAG in retro-orbital tissue
3. Associated disorders (see before)

## Clinical picture

Age: usually 11-15 yrs      Sex: ♀: ♂ = 5:1

### A) Local manifestations (Goiter):

Diffuse, soft, smooth surface, non-tender  $\pm$  bruit (upper poles)

### B) Systemic manifestations:

- Insomnia, irritability, nervousness, tremors,  $\uparrow\uparrow$  reflexes
- Heat intolerance,  $\uparrow\uparrow$  sweating, warm moist hands
- Loss of weight in spite of good appetite
- Palpitation, tachycardia, arrhythmia, big pulse volume
- Weakness (Myopathy), easy fatigability
- $\uparrow\uparrow$  Stool frequency (Diarrhea)
- Polyuria
- Menstrual irregularities, loss of libido
- RES hyperplasia (Spleen & LN)
- Patchy dermatopathy (pigmentation...)

# Lymphocytic thyroiditis

## (Hashimoto's thyroiditis)

### Definition

it is the commonest cause of acquired hypothyroidism

### Pathology

Autoimmune

### Etiology (= Evidence of immune nature)

1. Lymphocytic infiltration of the thyroid (T & B cells)

#### Thyroid autoantibodies

- Antiperoxidase antibodies
- Antithyroglobulin antibodies (ATA)
- Thyrotropin receptor blocking antibodies (TRBAbs)
- Thyroid stimulating immunoglobulins (TSI)
- Thyroid growth stimulating immunoglobulins (TGSI)

#### Associated disorders

- Type I autoimmune polyendocrinopathy (HAM syndrome)
- Type II autoimmune polyendocrinopathy (Thyroid, IDDM, Addison's disease)
- Pernicious anemia, vitiligo, alopecia, celiac disease
- Type I DM
- Myasthenia gravis
- Down, Turner, Klinefelter syndromes

### Clinical picture

A. Age: Any age usually > 6 yrs      Sex: ♀: ♂ = 5:1

B. Goiter: Diffuse, firm, non-tender (stationary / spontaneous regression)

B) Thyroid state:

- **Euthyroid:** most common at the onset
- **Hypothyroid:** many patients develop hypothyroidism within years
- **Hyperthyroid:** (Hashitoxicosis)

Associated disorders:

### Investigations

- Thyroid functions (↓↓ T<sub>4</sub> & T<sub>3</sub>, ↑↑ TSH, +ve Perchlorate test, US)
- Thyroid autoantibodies
- Biopsy: rarely indicated

### Treatment

- Periodic evaluation
- Sodium-L-thyroxine (*Eltroxin 50, 100 µg tablets*) in hypothyroidism

## Acquired Hypothyroidism (Juvenile)

### Definition

Symptoms of hypothyroidism appear after a period of apparently normal thyroid function (DD: Congenital hypothyroidism with late presentation)

### Etiology

#### 1. Autoimmune

- Lymphocytic thyroiditis "Hashimoto's thyroiditis" (Most common cause)
- Type II autoimmune polyendocrinopathy (Thyroid, IDDM)

#### 2. Iatrogenic

- Methimazole, propylthiouracil
- Thyroidectomy
- Radioactive Iodine ( $I^{131}$ )
- Irradiation (for malignancy & before bone marrow transplantation)
- Amiodarone
- Iodine exposure (potassium iodide, cough mixtures for asthma)

#### 3. Systemic diseases

- Nephropathic cystinosis
- Congenital nephrosis
- Histiocytosis

#### 4. Severe Iodine deficiency

#### 5. Thyroid hormone unresponsiveness (End organ resistance): usually "Euthyroid"

### Clinical picture

- A) Physical: Decelerated growth, delayed bone age, cold intolerance, constipation ± Goiter
- B) Mental: Sleepiness
- C) Sexual: Delayed puberty (precocious puberty may occur...)

### Investigations & Treatment "of the cause + Replacement therapy"

## Thyroiditis

### Etiology

#### 1. Lymphocytic thyroiditis "Hashimoto's thyroiditis" (most common cause)

#### 2. Acute suppurative thyroiditis

- Organism: Anaerobic ± aerobic
- Most common organisms: Strept. viridans & Staph. aureus
- Local manifestations: Swelling, redness, hotness, tenderness ± abscess formation
- Systemic manifestations: often absent
- Laboratory: leucocytosis, ↓↓ radioactive iodine uptake
- Thyroid function: usually normal (hyperthyroidism may occur due to escape of thyroid hormones)
- Treatment: Antibiotics ± abscess drainage

#### 3. Subacute non-suppurative thyroiditis (De Quervain disease)

- Etiology: viral infection (mumps...) usually on top of lymphocytic thyroiditis
- Local manifestations: vague pain & tenderness
- Systemic manifestations: low grade fever
- Thyroid function: usually hyperthyroidism (due to escape of thyroid hormones)
- Laboratory: ↑↑ ESR, ↓↓ radioactive iodine uptake
- Treatment: spontaneous remission (months) → Euthyroid → Hypothyroid state

#### 4. Chronic thyroiditis (TB, sarcoidosis)



**) Late Manifestations** (*The full-blown picture develop within 3-6 months*)

**a. Delayed mental development:** Social smile, recognition of mother...

**b. Delayed motor development:** Head support, sitting...

**c. Delayed sexual development** (but precocious puberty may occur...)

**d. Physical features:** (*The full-blown picture develop within 3-6 months*)

☒ **Vital signs**

- **HR:** Bradycardia
- **Temperature:** Hypothermia

☒ **Anthropometric measurements:** Short stature (Infantile proportion)

- US/LS: 1.7:1
- Height > span
- Short limbs

☒ **Systemic examination**

- Head: Delayed closure of anterior fontanel, open posterior fontanel
- Hair: Coarse, scanty, brittle and low anterior hair line
- Forehead: Short, wrinkled
- Eye: Puffiness of eyelids (Myxematous tissue)
- Nose: Depressed nasal bridge
- Tongue: Large, protruding (DD: Down syndrome)
- Lips: Pallor
- Teeth: Delayed dentition
- Neck: Short & thick  $\pm$  Goiter, When?
- Fat deposition above the clavicles
- Abdomen: Abdominal distension, umbilical hernia
- Skin: Dry, scaly?, cold?, pale?, yellowish ( $\uparrow\uparrow$  Carotene), myxedema (Non-pitting)
- Hands: Short & broad with short fingers & dorsal pad of fat
- Myopathy: Waddling gait
- CVS: Bradycardia, cardiomegaly, asymptomatic pericardial effusion

## Investigations

### Treatment "Replacement therapy"

**Sodium-L-thyroxine** (*Eltroxin 50, 100  $\mu$ g tablets*)

**Dose:** Neonates 10-15  $\mu$ g/kg/day, then 4-8  $\mu$ g/kg/day. Usual daily dose 100-300  $\mu$ g/d

**Duration:** Lifelong. To exclude transient causes, stop Rx at the age of 3 yrs for 3 wks  
 $\rightarrow$  Marked  $\uparrow\uparrow$  TSH in children with permanent hypothyroidism

**Monitoring of Rx:**

1. Clinical    Clinical improvement (maximum response occurs after 6 weeks).  
                   Overdose  $\rightarrow$  diarrhea, fever, tachycardia, sweating  
                   Assessment of height / 3 months  
                   Assessment of bone age / 6 months  
                   Assessment of IQ
2. Laboratory (T<sub>4</sub>, TSH)

**Side effects:**

- Overdose
- Craniosynostosis
- Pseudotumor cerebri

### Prognosis

Early diagnosis & treatment (Before the 3<sup>rd</sup> month of age)  $\rightarrow$  Better prognosis

## **Congenital Hypothyroidism** (Cretinism)

### **Definition**

Deficient production of thyroid hormone or defect in receptor activity (since birth)

### **Etiology** (Goiter = \*)

#### **(A) Primary hypothyroidism:**

1. **Thyroid dysgenesis** (most common cause = 85% of all cases)
  - Aplasia (thyroid scanning fail to detect any thyroid tissue)
  - Hypoplasia
  - Ectopic (Lingual, sublingual, subhyoid) variable onset of manifestations
2. **Defective hormone synthesis\*** (dyshormonogenesis = 10% of cases)
  - Iodide trapping
  - Organification
  - Coupling
  - Pendred syndrome
  - Deiodination defect
  - Storage (# Thyroglobulin synthesis)
3. **Thyroid hormone unresponsiveness\*** (End organ resistance = receptor defect) AD
  - $\uparrow\uparrow T_3 \& T_4 \rightarrow$  but clinically "Euthyroid" } DD: - TSH secreting pituitary tumor
  - Normal or  $\uparrow\uparrow$  TSH i.e., No TSH suppression } - Graves disease  $\downarrow\downarrow$  TSH
4. **Iodine deficiency\*(maternal)**
  - Mild-moderate  $\rightarrow \downarrow\downarrow T_4 \rightarrow \uparrow\uparrow TSH \rightarrow$  Goiter "Euthyroid"
  - Severe (endemic goiter)  $\rightarrow$  Goiter\*but decompensation "Hypothyroidism"
5. **Iodine exposure\***
  - Iodine containing antiseptics used in CS, NICU or surgical procedures "transient"
  - Amiodaron therapy (high iodine content)
6. **Maternal medications**
  - Radioactive Iodine ( $I^{131}$ )
  - Amiodarone, methimazole, propylthiouracil\*
7. **Maternal antibodies "transient"**  
 Transplacental passage of thyrotropin receptor blocking antibodies (TRBAbs)  $\rightarrow$  inhibits TSH binding to receptors (thyroid scanning fails to detect any thyroid tissue but US may show). TRBAbs may be present in mothers with auto immune thyroid disease (Graves, Hashimoto...)

#### **(B) Secondary:**

1. **TSH or TRH deficiency:** Isolated or multiple, pituitary or hypothalamic (T T I I I I E)
2. **TSH unresponsiveness:** ( $\downarrow\downarrow T_4$ ,  $\uparrow\uparrow$  TSH, No response to exogenous TSH)  
It may occur as a part of type Ia PHP
3. **TRH unresponsiveness:** TRH receptor defect. No response to TRH (No  $\uparrow\uparrow$  TSH)

### **Clinical picture** ♀: ♂ = 2:1

A) **At Birth:** Asymptomatic at birth (maternal  $T_4$ ). Diagnosis is now largely dependent on screening. Clinical manifestations usually appear in 1<sup>st</sup> few weeks

#### **B) Early manifestations of congenital hypothyroidism**

Prolonged gestational age  
 Prolonged physiologic jaundice > 2-3 weeks  
 Prolonged sleep  
 Poor feeding  
 Weak hoarse cry  
 Abdominal distension  
 Delayed passage of meconium & constipation  
 Open posterior fontanel  
 Hypothermia & mottling

### III Non-specific tests

1. **CBC:** Anemia in hypothyroidism
2. **Cholesterol:** ↑↑ in hypothyroidism
3. **Carotene:** ↑↑ in hypothyroidism
4. **Calcium:** ↑↑ in hyperthyroidism
5. **Glucose:** ↓↓ in hypothyroidism
6. **GH:** ↓↓ in hypothyroidism
7. **Basal metabolic rate (BMR):** ↑↑ in hyperthyroidism, ↓↓ in hypothyroidism
8. **X-rays:**
  - Bone X-ray: Delayed bone age  
Absent distal femoral ossific center
  - Chest X-ray: Pericardial effusion
9. **ECG:** Bradycardia, low voltage (Hypo-)
10. **EEG:** Low voltage

### IV Neonatal screening

Screening programs: from the 3<sup>rd</sup> to 7<sup>th</sup> days

	North America	Europe & Japan
<b>Technique (Heel prick)</b>	Measurement of T <sub>4</sub> (↓↓ < 5 µg/dL)	Measurement of TSH (↑↑ > 20 µU/mL)
<b>Advantages</b>	Identify: <ul style="list-style-type: none"> <li>▪ 1 ry hypothyroidism</li> <li>▪ 2 ry hypothyroidism</li> <li>▪ ↓↓ TBG</li> <li>▪ Patient with delayed ↑↑ in TSH</li> </ul>	Identify: <ul style="list-style-type: none"> <li>▪ 1 ry hypothyroidism</li> <li>▪ Subclinical hypothyroidism- (normal T<sub>4</sub>, ↑↑ TSH)</li> </ul>
<b>Disadvantage Missed cases</b>	Subclinical hypothyroidism (normal T <sub>4</sub> , ↑↑ TSH)	<ul style="list-style-type: none"> <li>▪ Patients with ↓↓ TBG</li> <li>▪ Delayed ↑↑ in TSH</li> <li>▪ Secondary hypothyroidism</li> </ul>

Regardless of the approach used in screening, some infants escape detection; clinicians should maintain their awareness of the early manifestations of hypothyroidism

#### No thyroid tissue by scanning:

- Aplasia
- Transplacental TRBAbs
- Trapping defect

#### Pendred syndrome:

Defect in organification due to defect in SO<sub>4</sub> transport protein

- Goiter
- Deaf-mutism
- Thyroid status: eu- or hypo-

Investigations: +ve perchlorate test

Rx: Thyroid hormone + Hearing aids

# Investigations of Thyroid Disease

## I For assessment of thyroid functions.

### 1. Serum total $T_4$ & $T_3$

- Normal values:  $T_4 = 4-11 \mu\text{g/dL}$   
 $T_3 = 60-200 \text{ ng/dL}$
- Affected by changes in TBG
- TBG is  $\uparrow\uparrow$  in:
  - Congenital
  - Estrogens (OCPs)
  - Neonates
  - Pregnancy
- TBG is  $\downarrow\downarrow$  in:
  - Congenital
  - Androgens
  - Liver failure
  - Congenital nephrosis

### 2. Free $T_4$ & $T_3$

The most accurate, not affected by TBG

### 3. Resin $T_3$ uptake

Known amount of radioactive  $T_3$  is added to the patient's serum to bind free TBG. The remaining unabsorbed  $T_3$  is absorbed by resin. It is a measurement of free TBG. Resin  $T_3$  uptake is  $\uparrow\uparrow$  in hyperthyroidism ( $\downarrow\downarrow$  free TBG)

### 4. Serum TSH (Normal values = $6 \mu\text{U/ mL}$ )

- TSH is  $\uparrow\uparrow$  in:
  - Primary hypothyroidism
  - TSH-secreting pituitary tumor
- TSH is  $\downarrow\downarrow$  in:
  - Hyperthyroidism
  - Secondary hypothyroidism (central)

### 5. TRH stimulation test (used in secondary hypothyroidism)

- $\uparrow\uparrow$  TSH & prolactin suggests hypothalamic lesion (not pituitary)
- No response occurs in pituitary lesions & TRH unresponsiveness (No  $\uparrow\uparrow$  TSH)

### 6. Radioactive iodine uptake ( $^{99m}\text{Tc}$ , $\text{I}^{123}$ , $\text{I}^{132}$ )

$\uparrow\uparrow$  Uptake  $\rightarrow$  Hyperthyroidism  
 $\downarrow\downarrow$  Uptake  $\rightarrow$  Hypothyroidism

## II For detection of the cause

### 1. Thyroid scanning ( $^{99m}\text{Tc}$ , $\text{I}^{123}$ , $\text{I}^{132}$ )

#### Indications

- Detection of ectopic thyroid gland e.g. lingual thyroid
- Detection of retrosternal goiter
- Solitary thyroid nodule; hot, cold or warm

### 2. Serum thyroglobulin

$\uparrow\uparrow$  in hyperthyroidism & differentiated thyroid carcinoma (tumor marker)

### 3. Thyroid US, CT & MRI

To detect size & location of the gland and the nature of solitary nodule (cystic/solid)

### 4. Fine needle aspiration cytology (FNAC) & biopsy

### 5. Thyroid autoantibodies

### 6. Detection of the cause of defective hormone synthesis

- Iodide trapping: Radioactive iodine uptake
- Organification: K-perchlorate competes with radioactive iodine for uptake & storage.  
In organification defects  $\rightarrow \uparrow\uparrow$  discharged iodine from the thyroid
- Coupling:  $\uparrow\uparrow$  MIT & DIT in thyroid biopsy
- Storage: absent thyroglobulin  $\rightarrow \downarrow\downarrow T_4 \rightarrow \uparrow\uparrow TSH \rightarrow$  Goiter
- Release "Deiodinase defect":  $\uparrow\uparrow$  MIT & DIT in blood & urine

# Thyroid Gland

## Physiology of thyroid hormones

### -Thyroid hormones:

- Tetraiodothyronine or Thyroxine ( $T_4$ )
- Triiodothyronine ( $T_3$ )

MIT= Moniodotyrosine  
DIT= Diiodotyrosine

### -Formation of thyroid hormones:

- Iodide trapping: against both electrical & concentration gradients
- Oxidation: oxidation of iodide to iodine "*Peroxidase*"
- Organification of iodine (= Iodination of tyrosine):  $\rightarrow$  MIT & DIT (inactive)
- Coupling:  $DIT + DIT \rightarrow T_4$   $DIT + MIT \rightarrow T_3$  "*Peroxidase*"
- Storage: bound to thyroglobulin in the colloid
- Release: by endocytosis & proteolysis of thyroglobulin  $\rightarrow$  release of  $T_4$  &  $T_3$   
NB: Free MIT & DIT are normally deiodinated; iodine is reused "*Deiodinase*"

### -Transport of thyroid hormones:

- The majority of  $T_3$  &  $T_4$  is bound to plasma proteins (*reserve or storage form*)
  - Thyroxine-binding globulin (TBG)
  - Albumin
  - Prealbumin
- The free part is the physiologically active
- $T_4$  is more abundant (50 times  $T_3$  concentration)
- 80% of circulating  $T_3$  is formed by deiodination of  $T_4$
- $T_3$  less bound shorter half-life more rapid action more active (3-5 times)
- $T_4$  is converted to  $T_3$  in peripheral tissues (cytoplasm)  $\rightarrow$  nuclear receptors

### -Control of secretion:

- TRH:  $\uparrow\uparrow$  TSH,  $\uparrow\uparrow$  prolactin
- TSH:  $\uparrow\uparrow$  cAMP  $\rightarrow$   $\uparrow\uparrow$  size,  $\uparrow\uparrow$  vascularity,  $\uparrow\uparrow$  function
- Feedback: by the free part of thyroid hormones
- Iodine:  $\downarrow\downarrow$  Iodine  $\rightarrow$   $\downarrow\downarrow$   $T_4$  &  $T_3$   $\rightarrow$   $\uparrow\uparrow$  TSH  $\rightarrow$  Goiter  
 $\uparrow\uparrow$  Iodine  $\rightarrow$  attenuate the TSH action on thyroid "Wolff-Chaikoff effect"

Trapping  
Organification  
Coupling  
Release

### -Action & side effects:

- Calorigenic  $\rightarrow$   $\uparrow\uparrow$   $O_2$  consumption,  $\uparrow\uparrow$  Metabolic rate (BMR),  $\uparrow\uparrow$  Heat production
- CHO  $\rightarrow$   $\uparrow\uparrow$  GIT absorption;  $\uparrow\uparrow$  glycolysis,  $\uparrow\uparrow$  glycogenolysis,  $\uparrow\uparrow$  gluconeogenesis
- Fats  $\rightarrow$   $\downarrow\downarrow$  cholesterol level ( $\uparrow\uparrow$  LDL receptors)
- Ptn  $\rightarrow$  Anabolic in physiologic dose, catabolic in large dose  
Myopathy (Myopathy & weakness occur in hyper- & hypothyroidism)  
Osteoporosis
- Bone  $\rightarrow$   $\uparrow\uparrow$  Bone age (in hypothyroidism)  $\rightarrow$  Delayed growth & bone age
- Vitamins  $\rightarrow$  Conversion of carotene to vitamin A  
 $\uparrow\uparrow$  Vitamin  $B_{12}$  absorption
- Blood  $\rightarrow$   $\uparrow\uparrow$  Erythropoiesis
- CVS  $\rightarrow$   $\uparrow\uparrow$  No & affinity of  $\beta$ -receptors in the heart ( $\uparrow\uparrow$  catecholamine effect)  
 $\uparrow\uparrow$  HR,  $\uparrow\uparrow$  stroke volume,  $\uparrow\uparrow$  systolic BP, peripheral VD,  $\uparrow\uparrow$  pulse pressure
- CNS  $\rightarrow$  Important for the rapidly growing brain (synapses, myelination)
- Growth  $\rightarrow$  Necessary for GH & IGF-1 synthesis & action
- Sexual maturation  $\rightarrow$  Delayed in hypothyroidism (precocious puberty may...)

#### Iodine metabolism:

Daily requirement: 30-150  $\mu$ g/day      Sources: near sea, iodized table salt

## Gynecomastia

### Definition

Enlargement of the male breast due to hypertrophy of the glandular tissue.

### Etiology

1. **Physiological**
  - a. **Neonatal:** Transplacental passage of maternal estrogens
  - b. **Pubertal** (65% of all ♂): ↑↑ aromatase activity. Bilateral or unilateral & tender
2. **Pathological**
  - a. **Endocrinal:** Male hypogonadism (Klinefelter syndrome)
  - b. **Liver cell failure** (↓↓ estrogen metabolism)
  - c. **Neoplastic:** Feminizing tumors (testicular & adrenal)
    - Prolactinoma
    - Bronchogenic carcinoma (Paramalignant syndrome)
  - d. **Drugs:** Estrogens, spironolactone, digitalis, cimetidine, ketoconazole
  - e. **Idiopathic**

## Cryptorchidism

### Definition

Failure of descent of one or two testes

**DD of empty scrotum:**

1. Absent testes
2. Retractable testes
3. Undescended testes

### Incidence

Term = 3.4%      Preterm = 30%      Spontaneous descent occurs in the majority  
If No descent by the age of 4 months, the testis will remain undescended

### Factors affecting testicular descent

1. **Hormonal**  
Testosterone, DHT & AMH
2. **Mechanical**  
Gubernaculum, epididymis & abdominal pressure

**Retractable testis:**

Brisk cremasteric reflex  
Testes can be brought down to the scrotum

### Classification

1. Abdominal
2. Inguinal
3. Gliding
4. Ectopic (Superficial inguinal, perineal)

### Investigation

1. Testosterone before & after hCG stimulation: to detect functioning testicular tissue & exclude anorchia
2. U/S, CT, MRI abdomen
3. Laparoscopy

### Complications

1. Infertility (Testicular pathological changes start to occur by 6-12 months)
2. Malignancy (1/40-80)
3. Psychological

### Treatment (Before 9-15 months, ideally at 6 months)

1. **Hormonal**
  - a. **hCG** (Pregnyl): IM 3000 IU/ wk for 4 weeks: or
  - b. **GnRH**
2. **Surgical** (Orchidopexy)

# Turner Syndrome

## Genetic Types

- ☑ Non-disjunction (most common): The X chromosome is usually of maternal origin—
- ☑ Mosaicism (better prognosis): 45, X / 46, XX

## Clinical picture

(A) At birth: Edema of dorsum of hands & feet

(B) Childhood:

- Short stature (mean = 143 cm)
- Webbing of the neck
- Widely spaced nipples
- Cubitus valgus (↑↑ carrying angle)
- Low posterior hair line
- Normal mentality (MR in 18%)
- Cardiac: Coarctation, bicuspid aortic valve
- Renal: Horseshoe, ectopic kidney...
- Thyroiditis (30%)
- IGT, Type II DM

(C) Puberty:

- Secondary sex characters fail to develop

## Investigations

1. Estrogen level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. Karyotyping (45, X)
4. U/S, Echocardiography, Thyroid profile

## Treatment

- hGH
- Estrogens: To induce the development of 2ry sex characters. Start at 11-12 yrs (Why?)
- Estrogen + Progesterone cyclic therapy:
  - Estrogen D1- D23
  - Progesterone D10- D23
  - No Rx D23-D30 → Withdrawal bleeding
- Ovum donation + IVF: ?? Fertility

# Female Hypogonadotropic-Hypogonadism

## Etiology

1. Hypopituitarism: Transcription factors & TTHHE
2. Isolated deficiency of gonadotropins:
  - Sporadic
  - Familial
3. Genetic defects:
  - Kallmann S (XLR, AR, AD) "hypogonadism, anosmia, mid-facial & renal defects"
4. Congenital syndromes
  - Laurence-Moon Biedl
  - Prader-Willi
5. Anorexia nervosa

## Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (anosmia in Kallmann syndrome)

## Investigations (as in 2ry ♂ hypogonadism)

## Treatment Constitutional delayed puberty should be ruled out

## Differential Diagnosis

**Constitutional delayed puberty:** "Not uncommon = 3 %"

**Diagnosis:** If no puberty (Testicular volume < 4 mL) by the age of 14-15 yrs & testosterone level < 50 ng/dL. It should be differentiated from hypogonadotropic-hypogonadism;

- **Family history:** +Ve
- **Single 8 A.M. Testosterone level:** is a good predictor of impending puberty
- **Nocturnal pulsatile LH secretion:** may be detected
- **GnRH stimulation test:** ↑↑ LH
- **Treatment:** Testosterone enanthate, 100 mg IM/4 wks, for 4-6 months

Value:

- Increase 2ry sex characters (relieves anxiety)
- May initiate puberty (↑↑ Growth & ↑↑ Bone age)
- DD: from Hypogonadotropic-hypogonadism (Diagnostic therapeutic test)

## Treatment

- Constitutional delayed puberty should be **ruled out**
- Established cases (pubertal changes regress after discontinuation of testosterone):
  - a. **Testosterone enanthate**, starting at 11-12 yrs  
Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks → Development of 2ry sex characters but with *small sized testes*
  - b. **hCG (Pregnyl):** IM 500-1000 IU, 3 times weekly → stimulates testicular growth & spermatogenesis. If testicular ↑↑ is not sufficient after 6-12 months, add:
  - c. **Human menopausal gonadotropin (HMG) "Humegon":** IM 37.5-150 IU, 3 times/ wk
  - d. **Episodic administration of GnRH:** programmable infusion pump (Very expensive)

## Prognosis

Spermatogenesis can be achieved after proper Rx (up to 2 yrs)

# Female Hypergonadotropic-Hypogonadism

## Etiology

1. **Turner syndrome (45, XO):** (1/2000)
2. **Noonan S:** Differences??
3. **XX Gonadal dysgenesis (Pure gonadal dysgenesis):** Gonads as Turner, No somatic features
4. **Mixed gonadal dysgenesis:** see before
5. **XXX female:** Non disjunction, No hypogonadism, learning & behavioral disorders
6. **XXXX & XXXXX female:** Hypogonadism + MR
7. **Resistant ovary syndrome:** FSH receptor defect
8. **Ovarian damage**
  - Radiotherapy & chemotherapy
  - Galactosemia
  - Denys-Drash syndrome
  - Ataxia telangiectasia
  - Immune ovarian failure

	Turner	Noonan
Sex	Only ♀	♀ & ♂
Genetics	Non-disjunction	AD
Cardiac	CoA / bicuspid aortic valve	PS
Mentality	MR in 18%	MR more common
Sexual Development	Hypogonadism	Delayed (2yrs)



## Clinical picture

1. **Onset:** Usually present as delayed puberty  
May be suspected at birth (Micropenis & small testes)
2. **Measurements:** Tall stature; span > height, LS > US (*Eunuchism*)
3. **Testes:** Absent or small (Prader Orchidometer)
4. **Secondary sex characters fail to develop:**
  - **Hair** (facial, axillary, pubic): scanty
  - **Acne:** absent
  - **Voice:** high pitched
  - **Fat distribution:** feminine (buttocks, breast)
  - **Penis & scrotum:** infantile
5. **Gynecomastia**
6. **Infertility** (Azoospermia)
7. **Picture of the cause**



## Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. hCG stimulation test: No response [Normally hCG → ↑↑ Testosterone at any age]
4. AMH & Inhibin level
5. Karyotyping (XXY...)
6. Azoospermia
7. Testicular biopsy (In Klinefelter \$: Hyalinized seminiferous tubules)

### Side Effects of sex steroids

- Lipid abnormalities
- Thromboembolism
- Acne
- HTN

## Treatment

- Long-acting testosterone **enanthate**, starting at 11-12 yrs (Why?)  
Dose: 50 mg IM / 3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg / 3-4 wks
- Intracytoplasmic sperm injection (ICSI): ?? fertility

# Male Hypogonadotropic-Hypogonadism

## Etiology

1. **Hypopituitarism:** Transcription factors & TTHLE
2. **Isolated deficiency of gonadotropins:**
  - Sporadic
  - Familial
3. **Genetic defects:**
  - Kallmann \$ (XLR, AR, AD) "hypogonadism, anosmia, mid-facial & renal defects"
  - DAX-1 gene mutation causing adrenal hypoplasia & impaired GnRH secretion
4. **Congenital syndromes**
  - Laurence-Moon Biedl
  - Prader-Willi

## Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (Microphallus in hypopituitarism, anosmia in Kallmann \$)

## Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↓↓ with absence of nocturnal pulsatile LH secretion
3. hCG stimulation test: ↑↑ Testosterone
4. GnRH stimulation test: Blunt GTH response (DD: Constitutional delayed puberty)
5. Other pituitary hormones (GH, ACTH) & imaging
6. DNA probes for different mutations (Kallmann \$)

# Hypogonadism

## Definition

- Delayed sexual development with no evidence of puberty by the age 13 in ♀ & 14 in ♂  
 - Causes include: Constitutional, hypogonadotropic & hypergonadotropic hypogonadism

Male Hypogonadism	Female Hypogonadism
<b>(A) Primary hypogonadism</b> (= Hypergonadotropic-hypogonadism) Testicular defect ↑↑ Gonadotropins	<b>(A) Primary hypogonadism</b> (= Hypergonadotropic-hypogonadism) Ovarian defect ↑↑ Gonadotropins
<b>(B) Secondary hypogonadism</b> (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓ Gonadotropins (FSH & LH)	<b>(B) Secondary hypogonadism</b> (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)

## Male Hypergonadotropic-Hypogonadism

### Etiology

1. **Congenital anorchia:** Testicular damage after sexual differentiation
2. **Defects of androgen production:** see before (46 XY-DSD)
3. **Rudimentary testes:** (AR or XLR) "Very small testes"
4. **Germ cell aplasia (De la Castillo \$ or Sertoli cell only\$):**
  - Leydig cells: normal → normal testosterone → normal sexual differentiation
  - Seminiferous tubules (absent Sertoli cells) → Small testes, azoospermia, infertility
  - No inhibin (normally secreted by Sertoli cell) → ↑↑ FSH with normal LH
5. **Klinefelter (47, XXY male):** (1/1000)
6. **45, X male:** Yp segment is translocated to another chromosome
7. **XX male:** Paternal X-Y Crossing over involving SRY gene
8. **XXX male:** Paternal X-Y Crossing over AND maternal X-X non-disjunction
9. **Noonan Syndrome:** (1/1000)
10. **Testicular damage**
  - Bilateral torsion (Vascular)
  - Surgical trauma during correction of cryptorchidism
  - Radiotherapy & chemotherapy
  - Acute orchitis: Mumps in pubertal ♂

### Noonan Syndrome:

- o Etiology: AD (variable expression)
- o Features of Turner \$ + Normal karyotyping + affecting ♀ & ♂
- o Short stature, neck webbing, cubitus valgus
- o CHD: PS
- o Facies: Hypertelorism, epicanthus, ptosis, micrognathia, antimongoloid slant, ear anomalies
- o Hypogonadism: Delayed puberty (2 yrs later)
  - ♂: Small testes, cryptorchidism
  - ♀: Premature ovarian failure
- o Mental retardation: 25%
- o Rx: hGH

### Klinefelter Syndrome:

#### Genetic types:

- Non-disjunction (most common)
- Mosaicism (better prognosis)
- Variants: XXXY, XXXXY (↑↑ Severity)

C/P: as in ♂ 1ry hypogonadism + some MR + learning disability + behavioral disorders

#### Investigations:

#### Complications:

Breast cancer, mediastinal germ cell tumors  
 Rx:

### Poly-Y male (47, XYY male):

No Hypogonadism  
 Aggressive antisocial behavior & violence

## Management of ambiguous genitalia:

1. It is medical & psychosocial **emergency** (Sex should be determined within 5 days)
  2. Birth **certificate** should not be filled out until sex is identified (avoid neuter names)
  3. **Team:** Pediatrician, endocrinologist, geneticist, gynecologist, urologist, psychologist
    1. Ambiguous genitalia may be the **clue** for diagnosis of life threatening conditions (CAH)
  5. Aim of Rx: To achieve **Cosmetically & functionally** normal external genitalia
  6. The sex of **rearing** depends on the appearance of **external** genitalia (phenotype) not chromosomal sex (genotype)
  7. Circumcision should be avoided in males with **hypospadias**
  8. It is easier to reconstruct external genitalia to create a functional ♀ rather than ♂
- (a) **Management of adrenal crises in cases of CAH**
- (b) **46, XX Intersex:** should be reared as ♀ **even if highly virilized**. They usually require feminizing genitoplasty (Reduction clitoroplasty, vaginoplasty...)
- (c) **46, XY Intersex:**
- o 5α Reductase deficiency: should be reared as ♂ because masculinization & spermatogenesis normally occur at puberty
  - o Testicular feminization S:
    - Should be reared as ♀
    - Orchiectomy **after** puberty
    - Estrogen replacement therapy (oral)
  - o Partial androgen insensitivity S:
    - Should be reared as ♀
    - **Early** orchiectomy is recommended (Source of virilization)
    - Estrogen replacement therapy (Oral)
  - o Reifenstein S: Should be reared as ♂
  - o Uterine hernia S: Orchidopexy & removal of Mullerian structures
  - o Micropenis: Testosterone enanthate 25-50 mg IM monthly (3-dose course)
- (d) **True hermaphroditism:** Depends on the external genitalia

### Diagnosis of Testicular feminization S

1. Pubertal ♀ with amenorrhea
2. Accidentally during heriotomy
3. At birth with antenatal karyotype?

### Completely feminized male

1. Deletion of short arm of Y
2. Pure gonadal dysgenesis (Swyer)
3. Testicular feminization S

### Mixed Gonadal Dysgenesis

**Gonads:** Testis on one side &  
Streak gonad on the other

**Genotype:** 46 XY/ 45 XO mosaicism

**Phenotype:** ambiguous\*, ♂ or ♀

**Rx:** - Feminizing genitoplasty (The usual)  
- Orchiectomy (Risk of malignancy)  
- Estrogen replacement therapy

### Phenotypes of 5α Reductase↓↓

1. Type 1: complete ♂
2. Type 2: ♂ micropenis
3. Type 3: ambiguous
4. Type 4: partial ♀
5. Type 5: complete ♀

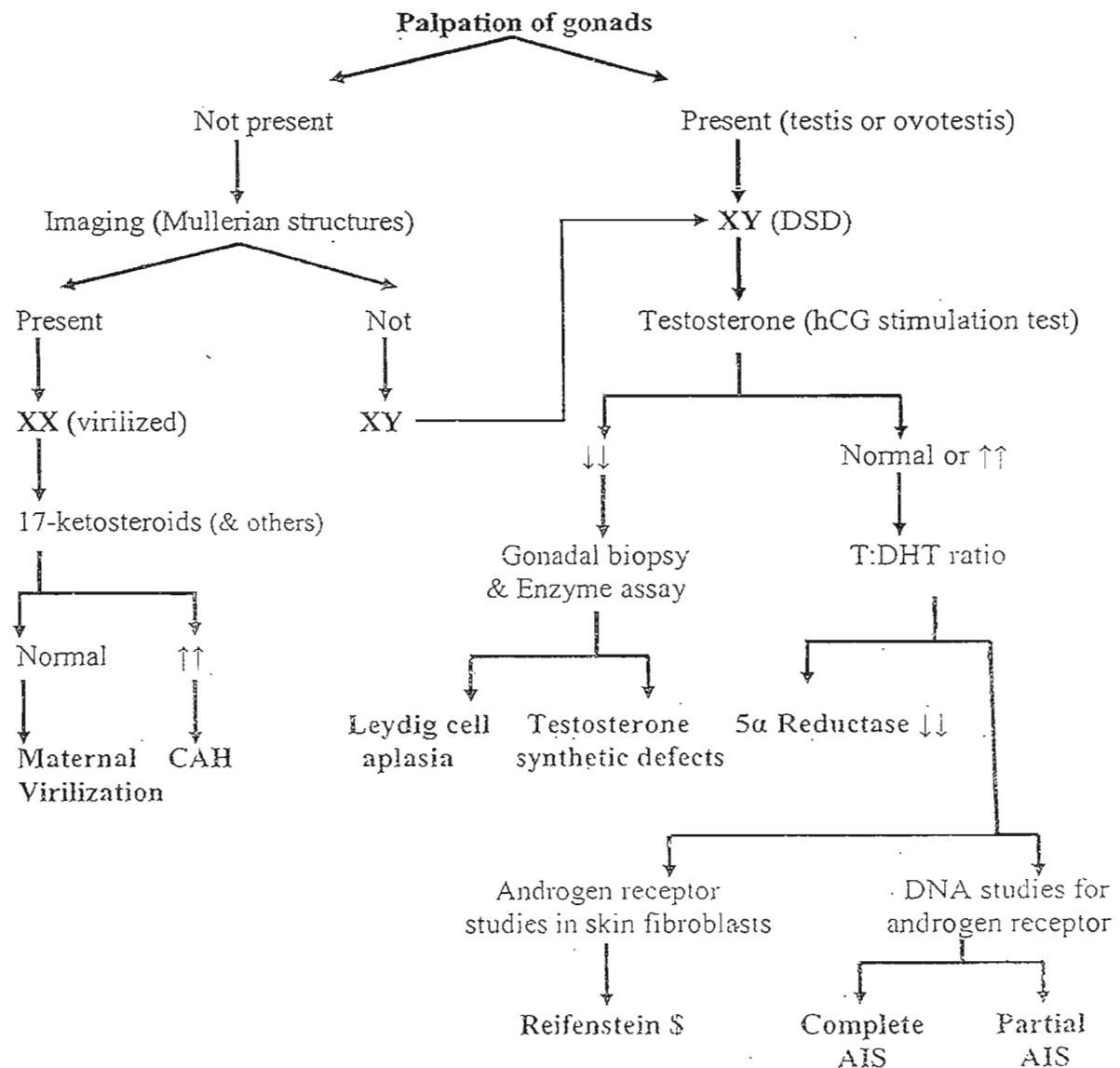
## Diagnostic approach to ambiguous genitalia:

### Clinical evaluation

- History: Consanguinity, family pedigree, inguinal hernia, infertility, similar conditions, unexplained neonatal deaths, maternal tumors, maternal drugs
- Examination:
  - Maternal virilization (deep voice, hirsutism)
  - Palpation of gonads (testes or ovotestes) in labioscrotal folds & inguinal canal
  - Phallic size, urethral opening, bimanual examination of uterus
  - Manifestations of CAH (FTT, vomiting, dehydration...)

### Investigations

- Karyotyping: to identify genotype (chromosomal sex)
- Serum electrolytes (Na, K), ABG, glucose, 17(OH) progesterone, urinary 17-ketosteroids
- Testosterone, DHT & T:DHT ratio before and after hCG stimulation, FSH, LH
- Pelvic US, CT, MRI for the presence of Mullerian structures (vagina, uterus)
- Genitogram
- Gonadal biopsy
- Open or laparoscopic exploration



## 46, XY Intersex (Genotype=XY, Phenotype = 3 possibilities??)

Causes	Defect	Gonads	Duct	Phenotype	Others
Defects in testicular differentiation	↓↓ Testosterone - No response to hCG Variable C/P according to the <u>time</u> of testicular failure				
Deletion of short arm of Y chromosome	No SRY	Streak	M	♀ No puberty	(<8w)
XY pure gonadal dysgenesis (Swyer)	SRY mutation	Streak	M	♀ No puberty	(<8w)
XY gonadal agenesis (8-12 weeks)	Testicular deg. AMH intact	No	No	Ambiguous (≈ near ♀)	(8-12 w) (Testicular regression \$)
Perineal anorchia (>20 weeks)	Testicular deg.	No	W	♂ No puberty	(>20 w) (Vanishing testes \$)
Prader-Willi \$	Ambiguous genitalia, Glomerulopathy (diffuse mesangial sclerosis), Wilms (usually bilateral). Rx: bilateral nephrectomy + RRT				
Wilms \$	Wilms tumor, Aniridia, Genitourinary malformation, Retardation				
Defects in testicular hormones	↓↓ Testosterone - No response to hCG				
Leydig cell aplasia/hypoplasia	LH receptor defect	Testis	W	♀ or mild virilization	Intact AMH
Steroidogenic defects	3β (OH) steroid dehydrogenase	*Testis	W	♀ or mild virilization No puberty	Salt losing
	20, 22 Desmolase	Testis	W		Salt losing
	17-α Hydroxylase	Testis	W		HTN
	17,20 Desmolase	Testis	W		
	17-Ketosteroid Reductase	Testis	W		
Ureterine hernia \$ (persistent Mullerian duct \$)	-Absent AMH -AMH receptor defect	Testis (80% Crypto-)	W M	♂ Normal virilization	Acc. discovered during hernia cryptorchidism
Defects in androgen action	Normal or ↑↑ Testosterone - Normal response to hCG - Intact AMH (↑↑ Testosterone: DHT ratio > 17 in 5α Reductase deficiency)				
5-α Reductase deficiency	↓↓ Dihydrotestosterone (DHT)	Testis	W	5 possibilities	Usually reared as ♂
Testicular feminization \$ (complete AIS)	End organ resistance	Testis	W	♀ attractive with 2ry sex characters	Amenorrhea Hernia > 50% Orchidectomy?
Partial androgen insensitivity \$ (AIS)	Lesser degree of androgen insensitivity	Testis	W	Ambiguous	Early Orchidectomy
Reifenstein \$ (Type of partial AIS)	Androgen receptor defect	Testis	W	Incomplete virilization ♂	Reared as ♂
Other causes					
Idiopathic	30% of male intersex				
Smith-Lemli-Opitz \$	Microcephaly, ptosis, ambiguous genitalia				

### Presentations of XY-intersex

1. Incomplete virilization    2. Ambiguous    3. Complete ♀

# Intersex & Ambiguous Genitalia

## Definition

**Intersex (Hermaphroditism):** Discrepancy between the morphology of gonads & external genitalia. The new proposed term is disorders of sex development (DSD)

**Ambiguous (atypical) genitalia:** Sex cannot be identified from external genitalia

**Virilized female:** Clitoromegaly, labial fusion, labial pigmentation

**Incompletely virilized male:** Small phallus, small  $\pm$  undescended testes, bifid scrotum, hypospadias

**Microphallus:** Penile size  $< 5^{\text{th}}$  for age; neonate with stretched penile length  $< 2$  cm

## Classification

(A) 46, XX Intersex (Female pseudohermaphroditism): most common form of DSD

(B) 46, XY Intersex (Male pseudohermaphroditism)

(C) True hermaphroditism (True gonadal intersex)

## 46, XX Intersex (Genotype = XX, Phenotype = virilized ♀)

Causes		Defect	Gonads	Duct	Phenotype	Others
Maternal virilization						
Virilizing maternal tumors (ovarian/adrenal)		Ovarian (androblastoma) Adrenal (adenoma)	Ovaries	M	Virilized ♀ -Clitoral ↑↑ -Labial fusion -Labial pigmentation	Maternal virilization
Androgenic drugs		Progestins	Ovaries	M		
Fetal virilization						
Congenital Adrenal Hyperplasia	21 Hydroxylase	Androgen excess	Ovaries	M	Virilized ♀	No Maternal virilization ↑↑ urinary 17ketosteroids
	11β Hydroxylase		Ovaries	M	Virilized ♀	
	3β (OH) steroid dehydrogenase		Ovaries	M	Mild virilization	
Placental Aromatase deficiency			Ovaries	M	Virilized ♀	
		Fetal adrenal androstenedione & testosterone are converted to estrone& estradiol by placental aromatase				
Other causes						
Idiopathic		Usually associated with GIT or genitourinary defects				

## True hermaphroditism (Both testicular & ovarian tissues are present)

### Gonads

Testis on one side & ovary on the other  
Or bilateral ovotestes

### Genotype

46 XX (70% of cases)  
46 XX/ 46 XY mosaicism  
46 XY

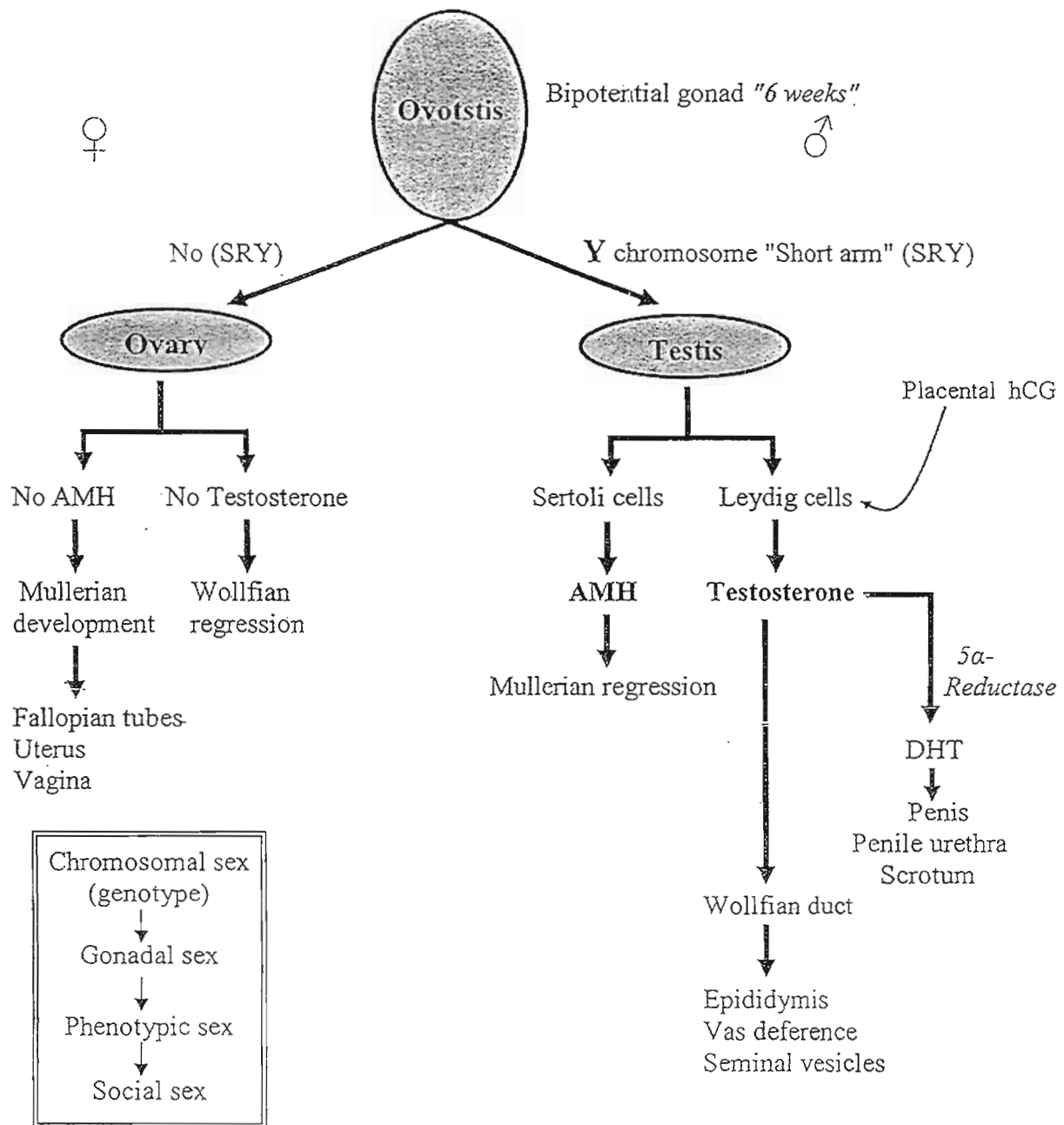
### Duct

Both Mullerian & Wolffian duct structures

### Phenotype

♂ or ♀ or ambiguous

# Normal Embryonic Sexual Differentiation



- Maleness require Y chromosome short arm (SRY gene) even with multiple X
- X chromosome carrying SRY → XX male syndrome
- SRY deletion / mutation → 46 XY intersex
- No Y chromosome → Ovary (2 X chromosomes are needed; otherwise streak gonads)
- Wolffian development depends on Y chromosome & testosterone
- Female phenotype is the default pathway
  - No Y → ovaries
  - No AMH → Mullerian development
  - No testosterone & DHT → Female external genitalia

**Clinical picture:**

- Tall stature (Adult height is normal or low)
- Advanced bone age & early puberty
- Acanthosis nigricans (hyperpigmented hyperkeratotic skin lesion usually in the post. neck or axilla). It is a clinical marker of insulin resistance & ↑↑ risk of type 2 DM

**Prevention:**

1. Change dietary habits & ↑↑ physical activity
2. Breast feeding → ↓↓ risk of obesity

**Treatment:**

1. Dietetic: ↓↓ CHO, ↓↓ fat, ↓↓ calories, ↑↑ fibers
2. Life style: ↓↓ TV watching, ↑↑ physical activity
3. Drugs "Not very promising"
  - ↓↓ *Food intake* → Sympathomimetics, MAO inhibitors
  - ↑↑ *Energy expenditure* → Ephedrine, caffeine
  - ↓↓ *Fat absorption* → Orlistat
4. Recombinant leptin: ↓↓ weight, ↑↑ energy expenditure
5. Surgical: gastropasty

**B) Endocrinal:**

- **Hypothalamic lesions:** Encephalitis, tumors (craniopharyngioma, optic glioma)
- **Frolich syndrome:** Dwarfism, polyphagia, obesity, DI, hypersomnia
- **Cushing syndrome**
- **Hypothyroidism**
- **Pseudohypoparathyroidism**
- **Stein-Leventhal \$:** Obesity, hirsutism, amenorrhea, infertility, polycystic ovaries, inverted FSH / LH ratio (Normally FSH > LH)

**C) Congenital syndromes:**

- **Laurance-Moon-Biedle \$:** Obesity, short stature, mental retardation, polydactyly, syndactyly, retinitis pigmentosa, hypogonadism
- **Beckwith-Wiedemann \$:** Fetal overgrowth, macrosomia, macroglossia, polycythemia, visceromegaly (HSM& nephromegaly), omphalocele, hemihypertrophy, hypoglycemia, characteristic ear lobe crease, ↑↑ risk of neoplasms (Wilms tumor)
- **Prader-Willi \$:** Hypotonia, hypogonadism, mental retardation, short stature, small hands& feet, early FTT followed by rapid weight gain (1-6 yrs), polyphagia & obesity  
*Genetics of Prader-Willi:*
  - Deletion of paternally acquired segment of chromosome 15
  - Maternal disomy (Both chromosomes 15 are from the mother)
 (NB: Paternal disomy of chromosome 15 → Angelman syndrome)

**C) Chromosomal:**

- |                     |                              |
|---------------------|------------------------------|
| ▪ Turner (XO)       | ▪ Klinefelter syndrome (XXY) |
| ▪ Down (Trisomy 21) | ▪ XXXXY syndrome             |

**Complications of obesity**

1. CVS → HTN, ischemic heart disease, hyperlipidemia& atherosclerosis
2. Respiratory → Sleep apnea, Pickwickian \$, restrictive hypoventilation
3. CNS → Pseudotumor cerebri, social& behavioral problems
4. GIT → Fatty liver, cholesterol gall stones, GERD
5. Endocrine → Insulin resistance, type 2 DM, early puberty, Stein-Leventhal \$
6. Joints → Slipped femoral epiphyses
7. Social & behavioral problems

**Approach to a case of obesity:**

Dietetic history, Stature, BP, Mentality, Syndromic



## B) Diagnosis of the etiology of Cushing syndrome:

### Hormonal:

- Plasma ACTH
  - a. ACTH dependent → ↑↑ ACTH
  - b. Non-ACTH dependent → ↓↓ ACTH
- CRH stimulation test:
  - a. ACTH dependent → ↑↑ ACTH & cortisol
  - b. Non-ACTH dependent → No response (Pituitary is suppressed)
- Dexamethasone suppression test [ $D_1$  30 µg/Kg/day qid,  $D_2$  120 µg/Kg/day qid]
  - a. ACTH dependent → ↓↓ Cortisol
  - b. Non-ACTH dependent → No response

### Imaging:

- X-ray: Osteoporosis, advanced bone age, ↓↓ thymic shadow
- Brain CT, MRI: Pituitary microadenoma
- Abdominal US, CT, MRI: adrenal adenoma

## Treatment

1. Adrenal tumors: surgical removal
 

<ul style="list-style-type: none"> <li>a. Benign → Subtotal adrenalectomy</li> <li>b. Malignant → Total adrenalectomy</li> </ul>	}	+ Replacement therapy (Cortisol & ACTH)
--	---	--
2. Pituitary adenoma (Cushing disease):
  - a. Pituitary irradiation (?? Hypopituitarism)
  - b. Surgical removal (Transphenoidal approach)
  - c. Total adrenalectomy: may be followed by the development of locally invasive pituitary tumor → ↑↑ ACTH → Hyperpigmentation (= *Nelson syndrome*)
  - d. Cyproheptadine (Centrally acting serotonin antagonist → # ACTH release)

# Obesity & Overweight

## Definition

- Obesity: BMI > 95<sup>th</sup>% for age & sex. (In adults BMI > 30 Kg/m<sup>2</sup>)
- Overweight: BMI = 85-95<sup>th</sup>% for age & sex
- Body mass index (BMI) = Weight (Kg) / Height<sup>2</sup> (meters)
- BMI also ↑↑ in body builders due to ↑↑ muscle bulk
- More than 22 millions children < 5 years are overweight

## Classification

### A) Exogenous obesity: [Most common]

#### Etiology: Multifactorial

- a. Gene-environment interaction
- b. Genetic control of energy expenditure (specific set point for body weight)
  - ↓↓ Energy expenditure → ↑↑ Risk of obesity
- c. Environmental
  - Type of food: ↑↑ calories, ↑↑ CHO, ↑↑ Fat, highly processed
  - Physical activity: TV watching, games, computers
- d. Heredity (parental obesity specially maternal, familial)
- e. Leptin deficiency or resistance: (↑↑ food intake & ↓↓ energy expenditure)

# Cushing Syndrome

## Definition

Increased level of cortisol with **hypertension** and characteristic pattern of **obesity**

## Etiology

### A) Exogenous Cushing Syndrome (Cushinoid Syndrome)\*:

Prolonged therapy with:

- ACTH
- Steroid

### B) Endogenous Cushing Syndrome:

#### ☒ ACTH dependent:

- a. **Cushing disease:** ACTH secreting pituitary adenoma (microadenoma)  
→ Bilateral adrenal hyperplasia (most common in children > 7 yrs)
- b. **Ectopic ACTH:** Pancreatic islet cell carcinoma, neuroblastoma, Wilms tumor

#### ☒ ACTH-independent (adrenal):

- a. **Functioning adrenocortical tumor:** in infancy (Malignant\* or benign)
- b. **Primary pigmented nodular adrenocortical disease:** multiple, small pigmented nodules
- c. **McCune-Albright syndrome** (autonomous hyperfunction)
- d. **Multiple Endocrine Neoplasia (MEN) type I**

## Clinical picture

- Characteristic obesity: Moon face, flushed plethoric face, doubled chin, trunkal, buffalo hump, thin limbs, striae rubra (abdomen & thigh).
  - Delayed healing of wounds
  - Osteoporosis → pathologic fractures and kyphosis
  - Muscle weakness & myopathy
  - Hyperglycemia
  - Short stature
  - Increased susceptibility to infection
- 
- Hypertension → Heart failure
  - Hypokalemia → Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany
- 
- Androgen excess → Hirsutism, acne, deep voice, accelerated growth & clitoromegaly
  - Adolescent female → Amenorrhea & hirsutism

## Investigations

### A) Diagnosis of Cushing Syndrome:

#### Laboratory:

- ↑↑ Na, ↓↓ K, ↓↓ H<sup>+</sup> (metabolic alkalosis)
- ↑↑ Glucose, OGTT
- CBC → ↑↑ RBC, ↑↑ PNLs, ↓↓ Lymphocytes, ↓↓ eosinophils

#### Hormonal:

- 3
- Cortisol level: loss of circadian rhythm then persistent elevation
  - ↑↑ Salivary cortisol level (screening)
  - ↑↑ Urinary cortisol & 17(OH) corticosteroids
  - Single dose dexamethasone suppression test (25 µg/Kg) → No ↓↓ in Cortisol level

# Hyperaldosteronism

## Definition

Increased level of Aldosterone

## Etiology

- A) **Primary hyperaldosteronism(Conn's):** [hypertension - hypokalemia - ↓↓ PRA]
- Adrenal adenoma
  - Adrenal hyperplasia
  - Glucocorticoid-suppressible hyperaldosteronism (AD):
    - Aldosterone secretion is regulated by ACTH → Hypertension
    - Dramatic response to glucocorticoids (Dexamethasone)
- B) **Secondary hyperaldosteronism:** [No hypertension - ↑↑ PRA]
- ↓↓ Effective plasma volume: Nephrotic \$, Liver cirrhosis, Heart failure
  - ↓↓ Renal perfusion: Renal artery stenosis
  - Bartter & Gitelman syndromes
- C) **Pseudohypoaldosternism** (End organ resistance) [Salt losing manifestations]
- D) **Syndrome of apparent mineralocorticoid excess** (Pseudohyperaldosternism):
- It is due deficiency of 11β (OH) steroid dehydrogenase which converts cortisol to cortisone  
 → ↑↑ Cortisol → ↑↑ mineralocorticoid receptors → Aldosterone like action  
 → Hypertension, hypokalemia (NB: Licorice also # this enzyme)

## Clinical picture

- A) **Primary hyperaldosteronism:**
- Hypertension: asymptomatic, headache, epistaxis, visual disturbances, heart failure, hypertensive encephalopathy (headache, vomiting, visual, coma, convulsions, ataxia)
  - Hypokalemia: Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany
- B) **Secondary hyperaldosteronism:** Picture of the cause
- C) **Pseudohypoaldosternism:** Salt losing manifestations
- D) **Pseudohyperaldosternism:** Hypertension, hypokalemia

## Investigations

**Laboratory:** ↑↑ Na, ↓↓ K, ↓↓H<sup>+</sup> (metabolic alkalosis), ↓↓ PRA

**Hormonal:** ↑↑ Aldosterone

Dexamethasone suppression test: Glucocortic suppressible hyperaldosteronism

**Imaging:** Abdominal US, CT & MRI: adenoma

**Adrenal vein catheterization & sampling:**

↑↑ Aldosterone in one adrenal vein → Adenoma

↑↑ Aldosterone in two adrenal veins → Hyperplasia

Exploratory laparotomy

### Liddle syndrome:

**Defect:** Activation mutation of Na epithelial channels

**C/P:** HTN, ↓↓ K, ↓↓ PRA

**Rx:** HTN & ↓↓ K

## Treatment

- A) **Primary hyperaldosteronism:**
- Adenoma → surgical removal
  - Hyperplasia → medical (spironolactone or amiloride), if failed → Surgery
  - Glucocorticoid-suppressible hyperaldosteronism → Dexamethasone
- B) **Secondary hyperaldosteronism:** Treatment of the cause
- C) **Pseudohypoaldosternism:** Supplementary salt

## I. Management of Acute suprarenal failure (crisis):

$$\text{Surface area} = \frac{4 \times \text{BW} + 7}{\text{BW} + 90}$$

### A) Fluid replacement:

- **Volume:** 2500-3000 ml/m<sup>2</sup>/day (*Shock + Deficit + Maintenance*)
- **Rate:** 1/4 → First 2 hours, the **remaining** is divided into:
  - 1/2 → Next 8 hours
  - 1/2 → Next 14 hours
- **Type:**
  - Blood glucose < 80 → G 10%: NS 1:1 or (G5%: NS = 2:1)
  - Blood glucose > 80 → G 5%: NS 1:1
- If the patient is shocked → Anti shock 20 ml/Kg (NS) over 30 min (subtracted)

### B) Steroid replacement:

- **Hydrocortisone IV:**
  - Bolus:** small children 50 mg  
Large children 100-150 mg
  - Maintenance:** 100 mg/m<sup>2</sup>/day divided / 6 hrs  
Then taper by decreasing the dose by 1/3 daily to reach the maintenance dose within 5 days
- **9-α fludrocortisol (Astonin H or cortilone):**
  - Dose:** 0.05-0.2 mg/day oral
  - Indications:** Severe salt losing manifestations



### Maintenance Therapy:

#### A) Hydrocortisone

- 10-15 mg/m<sup>2</sup>/day divided / 8 hrs
- Doubled or tripled during periods of stress or infection

#### B) 9-α fludrocortisol (Astonin H or cortilone)

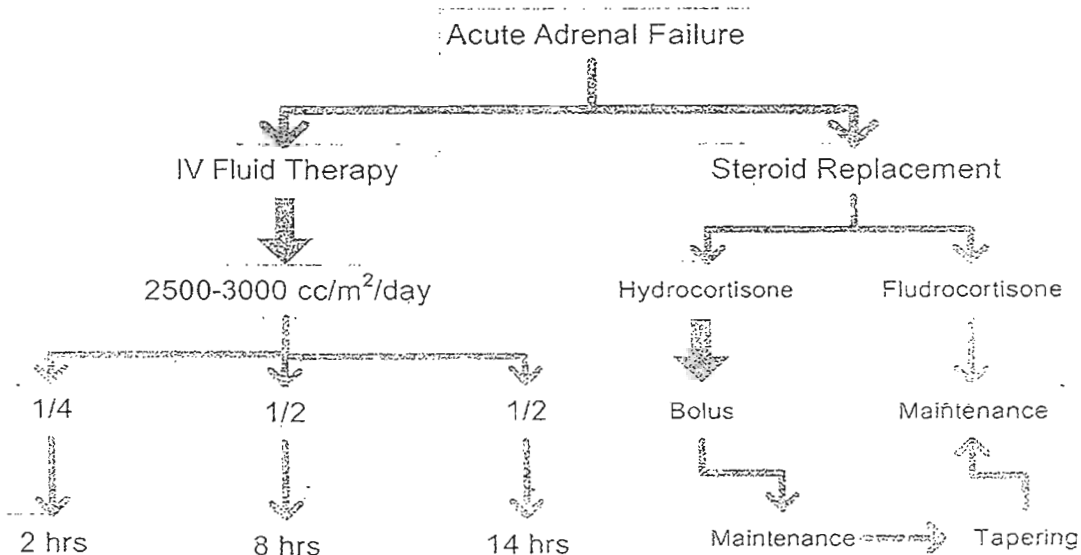
- 0.05-0.2 mg/day oral

### Monitoring of adequacy:

- Clinical improvement (hypotension), ↓↓ pigmentation
- Laboratory: ↓↓ PRA, normal electrolytes, 17 (OH) progesterone, DHEA level

### II. Treatment during surgery:

- Hydrocortisone IV 100 mg at the onset of anesthesia then 50 mg/ 6 hrs
- 9α fludrocortisol is given at night before operation



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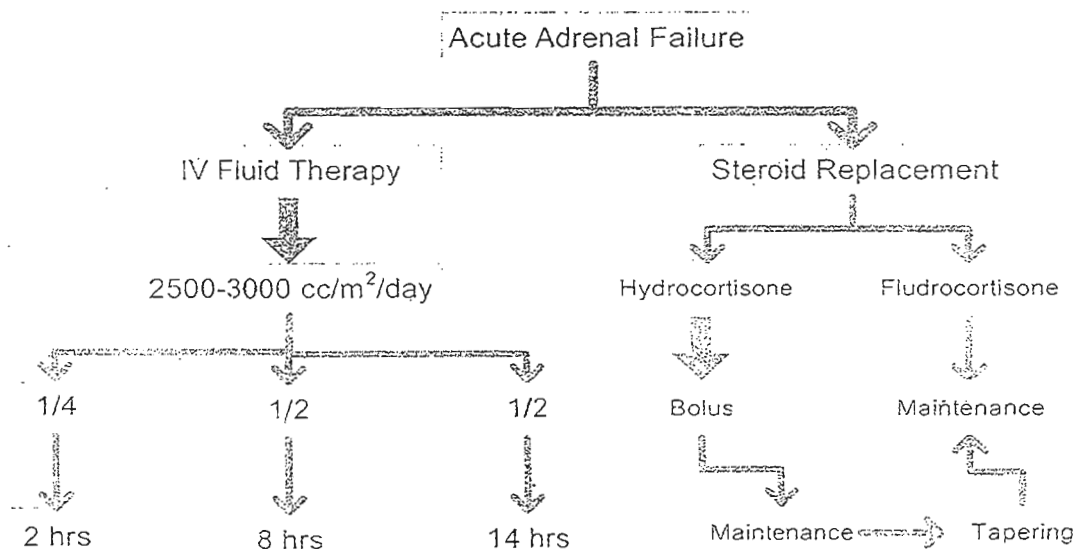
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## Clinical picture

**(A) Acute suprarenal failure (Crisis):** (as in cases of CAH, adrenal hemorrhage, Warehouse-Friderichsen syndrome, Addisonian crisis)

- Vomiting, abdominal pain, asthenia
- Dehydration, shock (poor peripheral perfusion, hypotension & acidosis)
- Hypotonia, coma, seizures ( $\downarrow\downarrow$  Na,  $\downarrow\downarrow$  glucose)

**Precipitating factors:** Infection, trauma, fatigue, surgery

**(B) Gradual onset of:**

- Asthenia, anorexia, abdominal pain, weight loss, FTT, hypotension
- Salt craving
- Pigmentation: Face, neck, axilla, nipple, areola, genitalia, pressure areas (absent in secondary causes, Why?)

## Investigations

**A) Laboratory:**

1.  $\downarrow\downarrow$  Na,  $\uparrow\uparrow$  K,  $\uparrow\uparrow$   $H^+$  (Metabolic acidosis)
2.  $\downarrow\downarrow$  Glucose
3. Plasma renin activity (PRA)  $\uparrow\uparrow$
4. Urinary Na  $\uparrow\uparrow$
5. CBC  $\rightarrow$  Neutropenia, lymphocytosis, eosinophilia
6. Investigations of the cause: Serum VLCFA, Anti-adrenal antibodies

**B) Hormonal:**

1. Plasma cortisol (*before & after* ACTH administration):  $\downarrow\downarrow$  (N = 5-25  $\mu\text{g/dL}$ )
2. Plasma ACTH
  - $\uparrow\uparrow$  in primary causes
  - $\downarrow\downarrow$  in secondary causes
3. ACTH stimulation test (Synacten IM daily for 3 days)  $\rightarrow$   
Plasma cortisol  $\uparrow\uparrow$  only in secondary causes
4. Plasma Aldosterone
5. Steroid precursors (DHEA, DHEA-S, androstenedione, testosterone, PRA, 17(OH) progesterone, 11-deoxycortisol)

**Most Definitive**

**C) Imaging:**

1. ECG: Hyperkalemia
2. Abdominal US: Calcification
3. CT & MRI

**ECG changes in  $\uparrow\uparrow$  K**

1.  $\uparrow\uparrow$  PR interval
2. Wide QRS
3. Tall peaked T wave\*\*
4. VF
5. Cardiac arrest

## Treatment

- *Once the diagnosis of acute suprarenal failure is suspected, immediate treatment should be started without waiting laboratory confirmation (rapidly fatal condition)*
- *Shock in acute suprarenal failure is not responsive to volume expansion & catecholamines unless glucocorticoids are used simultaneously*

- No need for mineralocorticoids in familial glucocorticoid deficiency & 2 ry causes
- No need for glucocorticoids in isolated aldosterone deficiency & pseudohypoaldosteronism
- Adrenal hemorrhage  $\rightarrow$  Vitamin K, C Blood transfusion
- Autoimmune  $\rightarrow$  exclude other immune and endocrinal disease

# Adrenocortical Insufficiency

## Definition

- Deficient production of cortisol &/or aldosterone or their action
- **Addison disease:** Acquired primary adrenal insufficiency

## Etiology

### (A) Primary:

#### 1. Adrenal aplasia or hypoplasia (X-Linked)

May be associated with Duchenne muscular dystrophy, mental retardation Or  
Hypogonadotropic-hypogonadism ( $\downarrow\downarrow$  GnRH) "DAX-1" mutation

#### 2. Familial glucocorticoid deficiency

- Isolated glucocorticoid deficiency (ACTH receptor defect) or as a part of
- Triple A syndrome: Alacrima- Achalasia- ACTH unresponsiveness

#### 3. Congenital adrenal hyperplasia (Impaired steroidogenesis)

- 20,22 Desmolase
- 21-Hydroxylase
- $3\beta$  (OH)steroid dehydrogenase
- Aldosterone synthase (isolated)

#### 4. Pseudohypoaldosteronism (End organ resistance)

Treated with supplementary salt (Mineralocorticoids are ineffective)



#### 5. Adrenoleukodystrophy (X-Linked)

- Peroxisomal disease  $\rightarrow$  accumulation of very long chain FA (VLCFA)  $\rightarrow$ 
  - Adrenal gland  $\rightarrow$  Insufficiency [Childhood (XL) or Neonatal (AR)]
  - White matter  $\rightarrow$  Academic deterioration, behavioral changes, dysarthria, dysphagia, visual disturbances, seizures, spasticity, ataxia.
- Addison disease may precede neurological manifestations by many years

#### 6. Mitochondrial diseases

Kearns-Sayer S (KSS)

#### 7. Cholesterol related disorders

- Wolman disease: Lysosomal acid lipase deficiency  $\rightarrow$  accumulation of cholesterol esters (HSM, steatorrhea)
- Smith-Lemli-Opitz syndrome (SLOS): Microcephaly, ptosis, ambiguous genitalia

#### 8. Immune:

- Isolated
- Type I autoimmune polyendocrinopathy "HAM" (Hypoparathyroidism, Addison, Mucocutaneous candidiasis)
- Type II autoimmune polyendocrinopathy (Thyroid, IDDM)

#### 9. Infection

- TB
- Meningococemia (Warehouse-Friderichsen)

#### 10. Neonatal adrenal hemorrhage

- Birth injury
- Asphyxia

#### 11. Iatrogenic

- Surgical removal
- Drugs: Ketokonazole, mitotane

### (B) Secondary:

1. ACTH or CRH deficiency: Isolated or multiple, pituitary or hypothalamic (T T I I I I E)
2. Abrupt cessation of steroid or ACTH therapy (Large dose + Long duration)??
3. Fetal adrenal gland suppression (Maternal Cushing or steroid therapy)

Disease	Treatment
Hydroxylase deficiency 0.1	<b>A) Glucocorticoids &amp; Mineralocorticoids:</b> <b>a. Hydrocortisone</b> <ul style="list-style-type: none"> <li>10-15 mg/m<sup>2</sup>/day divided / 8 hrs</li> <li>Doubled or tripled during periods of stress or infection</li> </ul> <b>b. 9-<math>\alpha</math> fludrocortisol</b> (Astonin H or cortilone) <ul style="list-style-type: none"> <li>0.05-0.2 mg/day oral</li> </ul> <b>c. Monitoring of adequacy:</b> <ul style="list-style-type: none"> <li>&gt; <b>Clinical</b> improvement (hypotension), <math>\downarrow\downarrow</math> pigmentation</li> <li>&gt; <b>Laboratory:</b> <math>\downarrow\downarrow</math> PRA, normal electrolytes, 17 (OH) progesterone, DHEA level</li> </ul> <b>B) Surgical</b> <ul style="list-style-type: none"> <li>Clitoris Resection</li> <li>Vaginoplasty</li> </ul> <b>C) Antenatal diagnosis:</b> Chorionic villous sample ( <u>Sex &amp; Genetic</u> ) <b>D) Antenatal Treatment:</b> of <u>affected female</u> fetus <ul style="list-style-type: none"> <li>Dexamethasone (20 <math>\mu</math>g/Kg of maternal weight) should be started at 6<sup>th</sup> gestational week</li> <li>Continue <u>only</u> in cases of <u>affected female</u> fetus (CVS)</li> </ul>
1- $\beta$ -Hydroxylase deficiency	<b>a. Hydrocortisone</b> <b>b. Anti-hypertensives</b>
- $\beta$ -(OH) Steroid hydrogenase deficiency	<b>a. Hydrocortisone</b> <b>b. Fludrocortisone</b> <b>c. Testosterone:</b> in incompletely virilized $\sigma$
0,22 Desmolase deficiency Lipoid adrenal hyperplasia	<b>a. Hydrocortisone</b> <b>b. Fludrocortisone</b> <b>c. Estrogens</b> for both $\sigma$ & $\phi$
7- $\alpha$ -Hydroxylase deficiency & 17, 20 Desmolase deficiency	<b>a. Hydrocortisone</b> <b>b. Anti-hypertensives</b> <b>c. <math>\phi</math>: Estrogens</b> <b>d. <math>\sigma</math>: Estrogens or Testosterone</b> (according to external genitalia)

- Intersex (Hermaphroditism): Discrepancy between the morphology of gonads & external genitalia. The new proposed term is disorders of sex development (DSD)
- Ambiguous genitalia: Sex cannot be identified from external genitalia (Atypical genitalia)
- Virilized female: Clitoromegaly, labial fusion, labial pigmentation
- Incompletely virilized male: Small phallus, small  $\pm$  undescended testes, bifid scrotum, hypospadias
- Microphallus: Penile size < 5<sup>th</sup> for age; neonate with stretched penile length < 2 cm



# Congenital Adrenal Hyperplasia

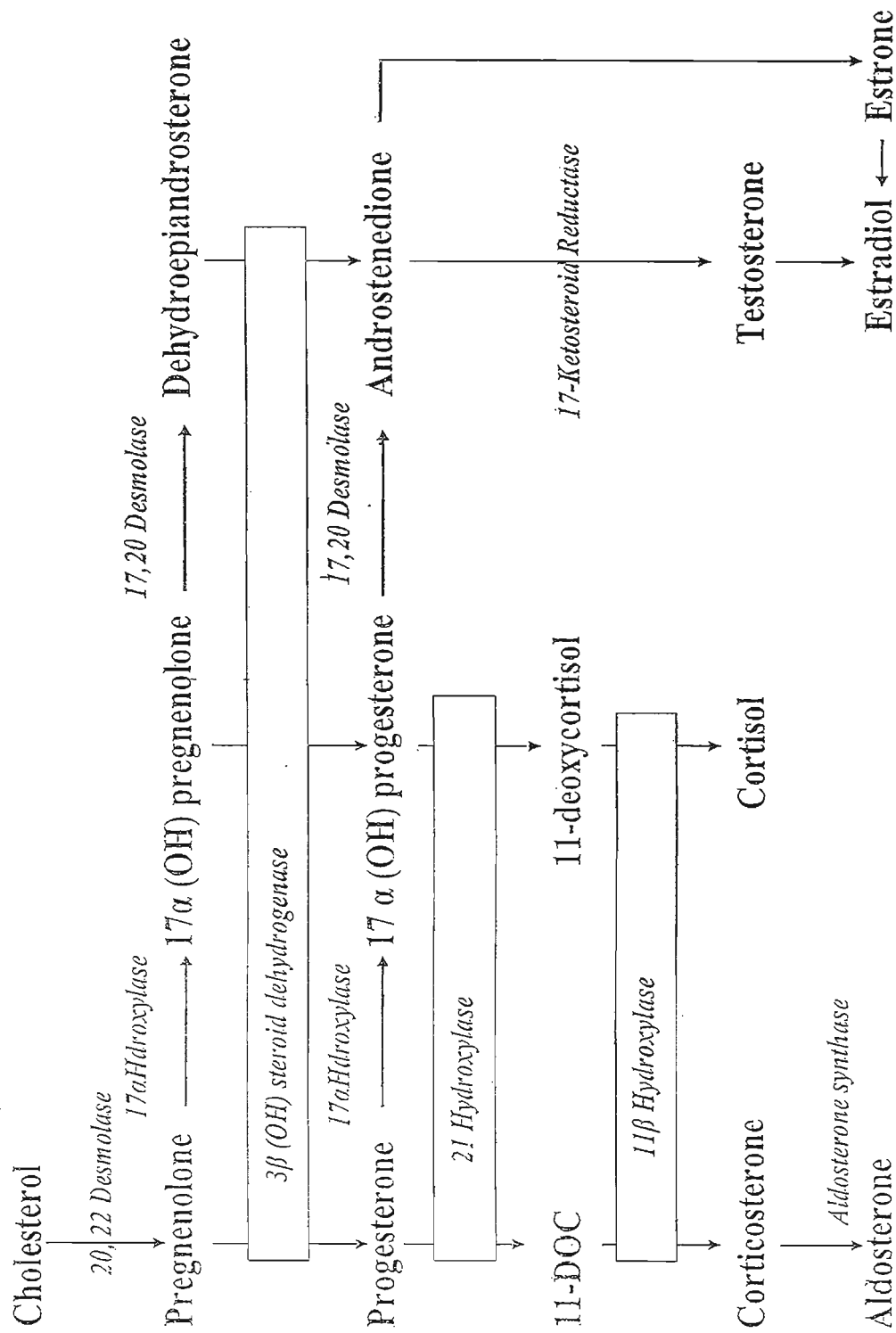
## Definition

AR disorders of cortisol biosynthesis → ↑↑ ACTH → adrenocortical hyperplasia →  
↑ production of intermediate metabolites → Variable C/P (Virilization, HTN, salt loss...)

## Classification

Type (Enzyme)	Biochemical Defects	C/P	Investigations
<b>21-Hydroxylase deficiency</b>  <b>90% of all cases</b>  <b>Classic</b> • Simple virilizing • Salt losing  <b>Non-classic:</b> • Onset • Mild • Severe • Androgenism in peripubertal ♀	Progesterone ↓ 11-DOC  17α Progesterone ↓ 11-Deoxycortisol	<b>A) Simple virilizing:</b> ♂: • Normal at birth • Isosexual precocious pseudopuberty (at 6 months) • 2 ry sex characters (Penis, scrotum, pubic hair, deep voice, ↑↑ bone age, masculinization) ♀: • Ambiguous genitalia • XX-intersex • Clitoromegaly, labial fusion, labial pigmentation • Heterosexual precocious pseudopuberty • ♂ 2 ry sex characters  <b>B) Salt-losing:</b> Virilization + Salt losing manifestations: (FTT, vomiting, dehydration, hypotension, shock, acidosis, RD, cyanosis)	↓↓ Na, ↑↑ K, ↑↑ H <sup>+</sup> (acidosis) ↓↓ Glucose ↑↑ PRA ↑↑ 17(OH)Prog. ↓↓ Cortisol ↓↓ Aldosterone ↑↑ DHEA ↑↑ U.Ketosteroid  ↑↑ Bone age US
<b>11β-Hydroxylase deficiency</b>  <b>Classic</b>  <b>Non-classic: milder</b>	11-DOC ↓ Corticosterone	<b>A) Virilization:</b> as before <b>B) Hypertension:</b> (11-DOC)	↑↑ DOC ↓↓ K ↓↓ PRA
<b>17α-OH Steroid Hydrogenase deficiency</b>	Pregnenolone ↓ Progesterone	<b>A) Salt losing:</b> ... <b>B) ♂:</b> Incomplete virilization <b>C) ♀:</b> Mild virilization	
<b>Δ<sup>4</sup>-Desmolase deficiency</b>  <b>Lipoid adrenal hyperplasia</b>	Cholesterol ↓ Prognenolone	<b>A) Salt losing:</b> ... <b>B) ♂:</b> Phenotypic female <b>C) ♀:</b> Normal (No puberty)	
<b>Δ<sup>5</sup>-Hydroxylase deficiency</b>	Pregnenolone →  Pregesterone →	<b>A) HTN</b> <b>B) ♂:</b> Phenotypic ♀ Or incomplete virilization <b>C) ♀:</b> Normal (No puberty)	↑↑ DOC ↓↓ K ↓↓ PRA
<b>Desmolase deficiency</b>	17(OH)Pregnenolone →  17(OH)Pregesterone →	<b>A) HTN</b> <b>B) ♂:</b> Phenotypic ♀ Or incomplete virilization <b>C) ♀:</b> Normal (No puberty)	

Virilization: 1, 2    HTN: 2, 5    Salt losing: 1, 3, 4



# Adrenal Glands

A) Adrenal cortex	B) Adrenal medulla
<p>1. <b>Zona Gomerulosa</b> → Mineralocorticoids</p> <ul style="list-style-type: none"> <li>• Aldosterone</li> <li>• Deoxycorticosterone (DOC) "Weak..."</li> </ul> <p>2. <b>Zona Fasciculata</b> → Glucocorticoids</p> <ul style="list-style-type: none"> <li>• Cortisol (10 mg/m<sup>2</sup>/d) } 17(OH)</li> <li>• Corticosterone } corticosteroids</li> </ul> <p>3. <b>Zona Reticularis</b> → Androgens</p> <ul style="list-style-type: none"> <li>• DHEA } 17-Ketosteroids</li> <li>• Androstenedione } (urine)</li> </ul>	<p><b>Products:</b> Catecholamines</p> <ul style="list-style-type: none"> <li>1. Adrenaline</li> <li>2. Noradrenaline</li> <li>3. Dopamine</li> </ul> <p>} <i>Vanillylmandelic acid (VMA)</i></p> <p>Urinary VMA ↑↑ in:</p> <ul style="list-style-type: none"> <li>• Pheochromocytoma</li> <li>• Neuroblastoma</li> <li>• Vanilla-containing foods</li> </ul>

## Mineralocorticoids

- ☒ **Control of secretion:**
  - **Renin-angiotensin system:** ↓↓ ECV & ↓↓ Renal perfusion, ↓↓ GFR
  - ↑↑ Serum K → ↑↑ Aldosterone
  - ACTH (Minor role)
- ☒ **Action:**
  - ↑↑ Na & H<sub>2</sub>O reabsorption
  - ↑↑ K & H<sup>+</sup> secretion

## Glucocorticoids

- ☒ **Control of secretion:**
  - ACTH & CRH: Circadian rhythm { Highest in the morning (waking-up)  
↓↓ to < 50% by midnight
  - Feedback
- ☒ **Action & side effects:**
  - CHO → ↑↑ Gluconeogenesis, ↓↓ Glucose utilization (3), IGT, DM
  - Fats → ↑↑ Lipolysis, redistribution (Facio-cervico-trunkal)
  - Ptn → Muscle (Wasting, myopathy)  
Bone (Osteoporosis) – Anti-vit. D effect (↓↓ Ca intestinal absorption)  
Skin (Poor wound healing, striae)
  - Mineralocorticoid effect → ↑↑ Na, ↑↑ H<sub>2</sub>O, ↓↓ K, ↓↓ H<sup>+</sup>
  - Blood → ↑↑ RBC, ↑↑ PNLs + ↓↓ Lymphocytes, ↓↓ Eosinophils
  - CVS → Permissive effect on catecholamines → Hypertension
  - CNS → ↓↓ Brain edema (Vasogenic), ↑↑ appetite, emotional lability, psychosis, memory disturbance
  - Growth → Direct inhibition of epiphyses, ↓↓ GH, ↓↓ IGF-1
  - Immune → ↓↓ TH<sub>1</sub> ↑↑ Risk of infection
  - Anti-inflammatory → ↓↓ Migration (Chemotaxis & diapedesis)  
↓↓ Permeability (Edema)  
↓↓ Antibody formation, ↓↓ Ag/Ab reaction  
↓↓ Proinflammatory cytokines (TNF-α, IL-1, IL-6)  
Stabilization of lysosomes

## Androgens

- ☒ Under the control of cortical androgen stimulating hormone (CASH)
- ☒ Growth promoting effect & androgenic effects

## Incomplete Precocious Puberty (Partial)

### Definition

Isolated precocity of one of the 2 ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂ without development of other signs of puberty. It is usually **transient**

Premature Thelarche	Premature Pubarche (Adrenarche)	Premature Menarche
<p><b>Definition</b> Isolated <b>breast</b> development</p> <p><b>Etiology</b> Sporadic (? Familial)</p> <p><b>Clinical picture</b> ▪ Age of onset: During the 1<sup>st</sup> 2 yrs. May at birth ▪ Course: Transient (3-5 yrs) Rarely progressive ▪ Bilateral or unilateral ▪ <b>Atypical (exaggerated) thelarche</b> ↑↑ bone age, U/S → ↑↑ Ovaries</p> <p><b>Investigations</b> ▪ FSH, LH, Estrogen: Normal ▪ Bone age: ± Advanced bone age ▪ Pelvic U/S: ± Ovarian cysts</p> <p><b>Treatment</b> Benign but F/U is needed as it may be 1<sup>st</sup> sign of precocious puberty</p>	<p><b>Definition</b> Isolated appearance of <b>sexual hair</b></p> <p><b>Etiology</b> Premature ↑↑ adrenal androgens</p> <p><b>Clinical picture</b> (♀ &gt; ♂) ▪ Sexual hair: pubic &amp; axillary hair ▪ <b>Atypical premature adrenarche:</b> Systemic androgenic effects (acne, ↑↑ bone age...) ▪ Course: Transient</p> <p><b>Investigations</b> ▪ FSH, LH, sex hormones: Normal ▪ DHEA: ↑↑ ▪ Bone age: ± Advanced bone age</p> <p><b>Treatment</b> Benign but F/U is needed as it may be 1<sup>st</sup> sign of precocious puberty</p>	<p><b>Definition</b> Isolated menses</p> <p><b>Clinical picture</b> ▪ 1-3 attacks of menstrual bleeding ▪ Course: Transient</p> <p><b>Investigations</b> ▪ FSH, LH, Estrogen: Normal ▪ Pelvic U/S: ± Ovarian cysts</p> <p><b>Treatment</b> Benign but F/U ...</p> <p><b>DD</b> (Vaginal bleeding) 1. Child abuse 2. FB 3. Vulvo-vaginitis 4. Uterine sarcoma</p>

### Precocious puberty in ♂:

- A) True precocious puberty
- B) Precocious pseudopuberty
  1. Isosexual
    - Gonadal: Leydig cell tumor, familial male precocious puberty
    - Adrenal: Virilizing adrenal tumor & CAH
    - Exogenous: Androgen
    - Gonadotropin-secreting tumors
  2. Heterosexual
    - Gonadal: Sertoli-cell tumor
    - Adrenal: Feminizing adrenal tumor
    - Exogenous: Estrogen
- C) Incomplete Precocious puberty  
Premature adrenarche
- D) Combined Precocious puberty
  - Familial male precocious puberty
  - CAH

### Precocious puberty in ♀:

- A) True precocious puberty
- B) Precocious pseudopuberty
  1. Isosexual
    - Gonadal: McCune-Albright S
  - Autonomous ovarian cyst, ovarian tumors
    - Adrenal: Feminizing adrenal tumor
    - Exogenous: Estrogen
  2. Heterosexual
    - Gonadal: ovarian tumors
    - Adrenal: Virilizing adrenal tumor & CAH
    - Exogenous: Androgen
- C) Incomplete Precocious puberty  
Premature thelarche, Adrenarche, menarche
- D) Combined Precocious puberty
  - McCune-Albright S
  - CAH

## precocious Pseudopuberty

Gonadotropin-Secreting Tumors	Familial male Precocious Puberty 1 <sup>st</sup> Leydig cell hyperplasia	McCune-Albright Syndrome
<p>I) <u>Hepatoblastoma</u>:</p> <p><u>Mechanism</u></p> <ul style="list-style-type: none"> <li>It secretes hCG → ↑↑ LH receptors → ↑↑ Leydig cells → ↑↑ Testosterone</li> <li>No spermatogenesis</li> </ul> <p><u>Clinical picture</u> (Only in ♂ ≈ 2 yrs)</p> <ul style="list-style-type: none"> <li>Isosexual precocious pseudopuberty</li> <li>Hepatomegaly</li> </ul> <p><u>Investigations</u></p> <ul style="list-style-type: none"> <li>hCG &amp; α-fetoprotein: ↑↑</li> <li>Plasma testosterone: ↑↑</li> <li>Gonadotropins (FSH &amp; LH): ↓↓ [In the past, ↑↑ LH due to cross reactivity with hCG]</li> <li>Testicular biopsy: Leydig cell hyperplasia</li> <li>Bone age: Advanced bone age</li> </ul> <p>II) <u>Other tumors</u>:</p> <ul style="list-style-type: none"> <li>Type: Teratoma, teratocarcinoma</li> <li>Site: CNS, mediastinum, gonads</li> </ul>	<p><u>Etiology</u> (AD)</p> <p><u>Mechanism</u> (Gonadotropin-independent)</p> <ul style="list-style-type: none"> <li>Activation mutation of LH receptors → ↑↑ Leydig cells → ↑↑ testosterone → ↑↑ bone age</li> <li>No spermatogenesis</li> </ul> <p><u>Clinical picture</u> (Only in ♂, 2 yrs)</p> <ul style="list-style-type: none"> <li>Isosexual precocious pseudopuberty</li> <li>True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined)</li> </ul> <p><u>Investigations</u></p> <ul style="list-style-type: none"> <li>Plasma testosterone: ↑↑</li> <li>Gonadotropins (FSH &amp; LH): ↓↓</li> <li>Testicular biopsy: Leydig cell hyperplasia</li> <li>Bone age: Advanced bone age</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>Ketokonazole (# Testosterone synthesis)</li> <li>GnRH analog (Leuprolide): in true puberty</li> </ul>	<p><u>Etiology</u></p> <p>Autonomous hyperfunction of glands</p> <p><u>Clinical picture</u> (Usually in ♀ ≈ 3 yrs)</p> <p>I) <u>Skin</u>: Pigmentation (Café-au-lait patches)</p> <p>II) <u>Skeletal</u>: Fibrous dysplasia</p> <p>III) <u>Endocrinal</u>:</p> <ol style="list-style-type: none"> <li>Gonads → Precocious pseudopuberty [Functioning follicular cyst → ↑↑ Estrogen] True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined)</li> <li>Thyroid → Hyperthyroidism</li> <li>Adrenal → Cushing syndrome</li> <li>Pituitary → GH excess (gigantism or acromegaly)</li> </ol> <p><u>Treatment</u></p> <p>☒ <u>Functioning ovarian cyst</u>:</p> <ul style="list-style-type: none"> <li>Surgery or aspiration</li> <li>Aromatase inhibitor (<i>Testolactone</i>)</li> <li>Anti-estrogen (<i>Tamoxifen</i>)</li> <li>GnRH analog (Leuprolide): (When??)</li> </ul> <p>☒ <u>Hyperthyroidism</u></p> <p>☒ <u>Cushing</u></p> <p>☒ <u>GH excess</u>: <i>Octreotide</i></p>

## True Precocious Puberty

Continuous GnRH stimulation: suppression

Idiopathic (Constitutional; functional)	Organic Brain lesion	PP following Radiotherapy
<p><b>Incidence</b> (♀: ♂ = 5-10:1)</p> <p>It is the cause of PP in 90% of ♀</p> <p>It is the cause of PP in <u>only</u> 25- 75% of ♂</p> <p><b>Etiology</b></p> <p>Sporadic (?? Familial)</p> <p><b>Clinical picture</b> (<i>Synchronous as normal</i>)</p> <p>☑ <b>Females:</b></p> <p>Breast enlargement → Pubic hair → Axillary hair → Menarche (+2ry sex characters)</p> <p>☑ <b>Males:</b></p> <p>Testicular ↑↑ → Thinning &amp; pigmentation of the scrotum → Penis ↑↑ → Pubic hair → Axillary hair (+2ry sex characters)</p> <p>☑ <b>Both ♀ &amp; ♂:</b></p> <p>Tall as children, Short as adults</p> <p>Gametogenesis: present (Pregnancy &amp; N. emissions)</p> <p>Mentality: compatible with chronologic age</p> <p>☑ <b>Course:</b></p> <p>Progressive (rapidly or slowly) or regressive</p> <p><b>Investigations</b></p> <p>1. Gonadotropins (FSH &amp; LH)</p> <p>↑↑ FSH &amp; LH with detected pulsatile LH</p> <p>GnRH stimulation: Brisk response ↑↑</p> <p>2. Sex hormones: ↑↑ (consistent with bone age)</p> <p>3. Bone age: Advanced bone age</p> <p>4. CT, MRI brain: to exclude I.C. lesions (♂)*</p> <p>5. Pelvic U/S: ↑↑ Ovaries, uterus ± ovarian cysts</p> <p><b>Treatment</b></p> <p>GnRH analog (<i>Leuprolide</i>): 0.25-0.3 mg/Kg IM every 4 wks (Other routes = intra nasal, SC)</p> <p><b>Side effects:</b> Recurrent sterile fluid collection at injection sites</p> <p><b>Effects:</b> ↓↓ GTH &amp; sex hormones + ↓↓ growth rate to normal + ↑↑ adult height</p> <p>Regression of 2 ry sex characters (breasts, menses, testicular size, pubic hair)</p>	<p><b>Incidence</b></p> <p>It is the cause of PP in 10% of ♀</p> <p>It is the cause of PP in 25- 75% of ♂</p> <p><b>Etiology</b></p> <p>1. Hypothalamic hamartoma</p> <p>2. Intracranial lesions (involving the hypothalamus)</p> <p>☑ TB meningitis</p> <p>☑ Encephalitis</p> <p>☑ Tumors (astrocytoma, ependymoma...)</p> <p>☑ Trauma</p> <p>☑ Tuber sclerosis</p> <p>☑ Neurofibromatosis (optic glioma)</p> <p>3. Pineal region tumors (germinoma, astrocytoma)</p> <p><b>Clinical picture</b></p> <p>☑ <b>Endocrinal:</b> may precede the IC lesion</p> <p>☑ <b>Picture of the cause:</b> ↑↑ ICT, visual field...</p> <p>☑ <b>Hypothalamic syndrome:</b></p> <p>☑ Hypothermia, hyperthermia, adipisia, DI</p> <p>☑ Obesity, cachexia</p> <p>☑ Hypersomnia</p> <p>☑ Gelastic seizures (unnatural laughing)</p> <p><b>Investigations</b> as in constitutional precocious P.</p> <p><b>Treatment</b> GnRH analog (<i>Leuprolide</i>)</p> <p>Rx of the cause</p>	<p><b>Mechanism</b></p> <p>Radiotherapy → True Precocious Puberty</p> <p><b>Clinical picture</b></p> <p>1. Precocious puberty: ↑↑ growth</p> <p>2. GH &amp; TSH deficiency: ↓↓ growth</p> <p>3. Net result: Normal growth</p> <p><b>Treatment</b></p> <p>☑ GnRH analog (<i>Leuprolide</i>): 0.25-0.3mg/Kg IM every 4 wks</p> <p>☑ GH &amp; Thyroid supplementation</p> <p><b>Hypothyroidism &amp; precocious puberty</b></p> <p><b>Incidence</b></p> <p>Hypothyroidism usually cause delayed puberty*</p> <p>Precocious puberty may occur in severe, untreated 1ry hypothyroidism of long duration</p> <p><b>Mechanism &amp; C/P</b></p> <p>TSH &amp; GTH (LH &amp; FSH) have identical α-chain</p> <p>↓ T<sub>3</sub>, T<sub>4</sub> → ↑↑ TSH → ↑↑ FSH receptors → ↑↑ Estrogen → ↑↑ Breast &amp; Bleeding (menses)</p> <p>No ovulation</p> <p>☑ <b>Females:</b></p> <p>☑ <b>Males:</b></p> <p>↑↑ Sertoli cells → ↑↑ Testicular size</p> <p>No ↑ of Leydig cells → No ↑↑ testosterone</p> <p>No virilization</p> <p><b>Investigations</b></p> <p>1. TSH &amp; prolactin: ↑↑</p> <p>2. Gonadotropins (FSH &amp; LH): ↓↓</p> <p>3. CT, MRI brain: ↑↑ Sella</p> <p>4. Pelvic U/S: Ovarian cysts</p> <p><b>Treatment</b> Thyroid supplementation (↓ TSH)</p>

# Precocious Puberty

## Definition

The appearance of 2ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂

	True Precocious Puberty	Precocious Pseudopuberty
Synonyms	Central (intra-cranial) Gonadotropin dependent	Peripheral (extra-cranial) Gonadotropin independent
H-H-G	Active	Inactive
FSH & LH	↑↑	↓↓
Gonads	Active	Inactive
Gametogenesis	Present	Absent
2ry sex characters	Isosexual لازم	Isosexual or heterosexual
GnRH stimulation	↑↑ LH & FSH	No ↑↑ LH & FSH

Precocious pseudopuberty → ↑↑ bone age → activation of HHG axis → True Precocious puberty (**Combined** Gonadotropin dependent & Gonadotropin independent Puberty)

## Etiology

### I) True Precocious Puberty:

- A) Idiopathic (constitutional, functional)
- B) Organic brain lesions
  - Hypothalamic hamartoma
  - Intracranial lesions
  - Pineal region tumors
- C) Radiotherapy
- D) Hypothyroidism

### True precocious puberty:

- ♀ → 80% of cases are idiopathic  
♂ → 80% of cases are pathologic

### II) Precocious Pseudopuberty:

		Gonadal	Adrenal	Exogenous
Female	Isosexual (Feminizing)	<ul style="list-style-type: none"> <li>• McCune-Albright S</li> <li>• Autonomous ovarian cyst</li> <li>• Ovarian tumors                             <ul style="list-style-type: none"> <li>➢ Granulosa cell tumor</li> <li>➢ Teratoma</li> </ul> </li> </ul>	Feminizing adrenal tumor	Estrogens
	Heterosexual (Virilizing)	<ul style="list-style-type: none"> <li>• Ovarian tumors e.g., Androblastoma</li> </ul>	<ul style="list-style-type: none"> <li>• Virilizing adrenal tumor</li> <li>• CAH</li> </ul>	Androgens
Male	Isosexual (Virilizing)	<ul style="list-style-type: none"> <li>• Leydig cell tumor</li> <li>• Familial male precocious P.</li> </ul>	<ul style="list-style-type: none"> <li>• Virilizing adrenal tumor</li> <li>• CAH</li> </ul>	Androgens
	Heterosexual (Feminizing)	<ul style="list-style-type: none"> <li>• Sertoli cell tumor</li> </ul>	Feminizing adrenal tumors	Estrogens

In ♂, hCG secreting tumors (Hepatoblastoma, CNS, mediastinum) → Isosexual precocious pseudopuberty

### III) Incomplete Precocious Puberty:

- Premature thelarche
- Premature adrenarche
- Premature menarche

### IV) Combined Puberty:

- Congenital adrenal hyperplasia
- McCune-Albright S
- Familial male precocious puberty

# Diabetes Mellitus

## Definition

It is a primary disturbance of CHO metabolism resulting from insulin deficiency, insulin resistance or both and characterized by hyperglycemia as a cardinal biochemical feature with secondary disturbance of fat & protein metabolism

## Classification

### A) Type 1 DM: (formerly called IDDM or juvenile diabetes)

Caused by insulin deficiency

### B) Type 2 DM: (formerly called NIDDM or adult-onset diabetes)

Caused by insulin resistance with some degree of failure of insulin secretion

### C) Secondary diabetes:

- Endocrinal: acromegaly, Cushing, hyperthyroidism, glucagonoma, somatostatinoma, pheochromocytoma
- Exocrine pancreas: Trauma, tumors, resection, hemochromatosis, Cystic fibrosis, pancreatitis, Pearson marrow pancreas syndrome
- Infections: CMV, congenital rubella, HUS
- Drugs: steroids, diazoxide, thiazides,  $\beta$ -adrenergic agonists, cyclosporine
- Genetic defects of  $\beta$ -cell function: MODY-1, MODY-2, MODY-3, MODY-4, 5, 6
- Genetic defects in insulin action: Type A insulin resistance, lipodystrophic DM
- Genetic syndromes:
  - Prader-Willi, Laurence-Moon-Beidel
  - Huntington chorea, myotonic dystrophy, Friedreich ataxia
  - Wolfram (DIDMOAD)
  - Down, Turner, Klinefelter

### D) Gestational diabetes: Caused by

- Alimentary glucosuria
- Renal glucosuria
- Production of anti-insulin: estrogen, progesterone, cortisol, placental insulinase enzyme, human placental lactogen (hPL)

### E) Neonatal diabetes:

- Transient: a-Without recurrence    b-With recurrence 7-20 yrs later  
*Onset*: 1<sup>st</sup> week of life    *Course*: spontaneous resolution within weeks/months  
*Etiology*: functional immaturity of  $\beta$ -cells  
*C/P*: SGA, hyperglycemia, glucosuria, dehydration, metabolic acidosis  
*Rx*: Intermediate-acting insulin 1-2 U/Kg/day bid
- Permanent: pancreatic agenesis

### F) Impaired glucose tolerance (metabolic state intermediate between normal & DM)

## Diagnostic criteria

Impaired glucose tolerance	Diabetes mellitus
Fasting plasma glucose = 110-125 mg/dL	Fasting plasma glucose $\geq 126$ mg/dL
Or	Or
2 hr plasma glucose (OGTT) $< 200$ mg/dL	2 hr plasma glucose (OGTT) $\geq 200$ mg/dL
But $\geq 140$ mg/dL	Or
	Random plasma glucose $\geq 200$ mg/dL
	+ symptoms of DM (polyuria, polydipsia, loss of weight, glucosuria, ketonuria)



# Type 1 Diabetes Mellitus

## Definition

Diabetes mellitus caused by insulin deficiency due to destruction of pancreatic  $\beta$ -cells.

## Etiology & Pathogenesis

Autoimmune response against  $\beta$ -cells in a **genetically predisposed** individual triggered by an **environmental factor**

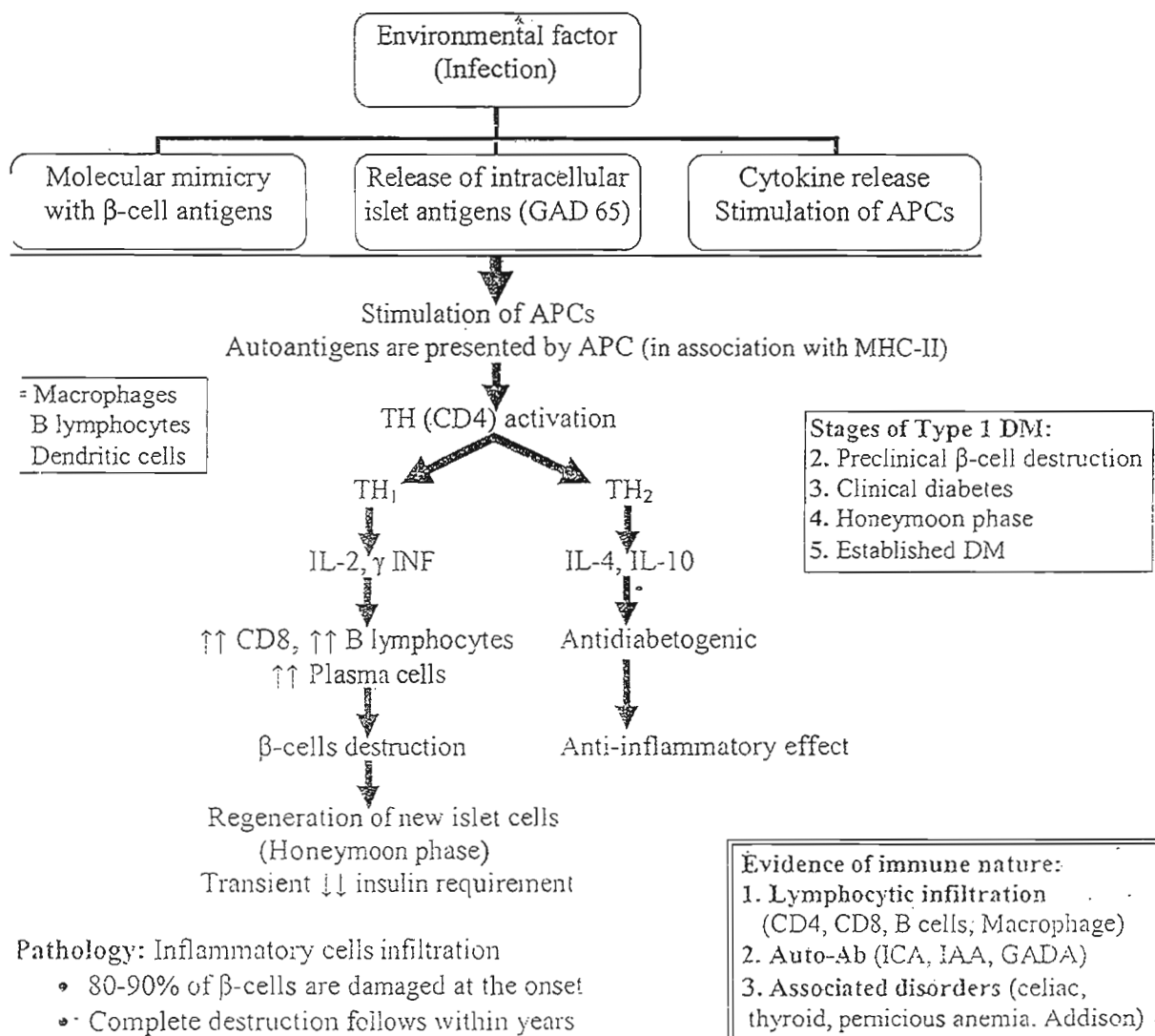
### A) Genetic predisposition:

- HLA-DR3 or HLA-DR4  $\rightarrow$   $\uparrow\uparrow$  Risk 2-3 folds
- Both HLA-DR3 & HLA-DR4  $\rightarrow$   $\uparrow\uparrow$  Risk 7-10 folds
- Absence of aspartate at position 57 of HLA-DQ  $\beta$ -chain  $\rightarrow$   $\uparrow\uparrow$  Risk 100 folds
- Presence of arginine at position 52 of HLA-DQ  $\beta$ -chain  $\rightarrow$   $\uparrow\uparrow$  Risk

### B) Environmental factors:

- Viral infections: Coxsackie B3, B4, mumps, rubella, CMV
- Seasonal: autumn & winter (?? Due to  $\uparrow\uparrow$  risk of viral infections )
- Diet: cow's milk (molecular mimicry between bovine albumin & islet antigen 69)
- Chemicals: Rodenticides

### C) Autoimmune factors (=Pathogenesis of $\beta$ -cell destruction):



**Prediction** (?? Done for high risk children)

- HLA typing (DR3, DR4)
- Autoantibodies:
  - ☑ Islet cell antibody (ICA)
  - ☑ Insulin autoantibodies (IAA)
  - ☑ Glutamic acid decarboxylase (GAD65) antibodies (GADA)

**Prevention**

- Breastfeeding
- Vitamin D supplementation during infancy (?? Immunosuppressive effect)
- Immunosuppressives (Immunotherapy in *new-onset type 1 DM*):
  - ☑ Cyclosporin, azathioprine, prednisone, antithymocyte globulin (ATG)
  - ☑ Anti-CD3 monoclonal Ab (OKT3)

**Pathophysiology**

- **Hyperglycemia:**  $\downarrow\downarrow$  Insulin  $\rightarrow \downarrow\downarrow$  Uptake & utilization &  $\uparrow\uparrow$  Production of glucose
- **Glucosuria:** when the renal threshold (180 mg/dL) is exceeded  $\rightarrow$  osmotic diuresis  $\rightarrow$  **polyuria & polydipsia**
- **Hunger & polyphagia:**  $\downarrow\downarrow$  Glucose uptake by the satiety center
- **Weakness:**
  - Inhibition of Krebs cycle ( $\downarrow\downarrow$  ATP): due to  $\downarrow\downarrow$  oxaloacetate  $\rightarrow$   $\downarrow\downarrow$  glycolysis
  - Catabolic state
- **Delayed wound healing**
  - $\downarrow\downarrow$  Lipogenesis &  $\uparrow\uparrow$  lipolysis  $\rightarrow \uparrow\uparrow$  FFA  $\rightarrow$  **Hypertriglycerolemia & fatty liver**
  - $\uparrow\uparrow$  FFA  $\rightarrow \uparrow\uparrow$  FA oxidation  $\rightarrow \uparrow\uparrow$  acetyl-CoA  $\rightarrow$  **Hypercholesterolemia**
  - $\rightarrow$  **Ketogenesis**
- **Acidosis:** due to ketosis (ketonemia & ketonuria)  $\rightarrow$  Diabetic ketoacidosis (DKA)
- **Coma:** due to dehydration, hyperosmolality, acidosis & electrolyte disturbances
- **Hyperosmolality:** due to dehydration & hyperglycemia
  - Osmolality =  $2 \times \text{Na} + \text{Glucose} / 18 + \text{BUN} / 3$  ( $N = 285-295 \text{ mOsmol/Kg H}_2\text{O}$ )
  - Effective osmolality =  $2 \times \text{Na} + \text{Glucose} / 18$  (Urea is not an effective osmole)
- Hyperglycemia  $\rightarrow$  Shift of  $\text{H}_2\text{O}$  from IC to EC space  $\rightarrow$  **Hyponatremia**

**Clinical picture**

- Age:** usually 7-15 yrs    **Sex:** ♀: ♂ = 1:1    **Seasonal Variation:** more in winter
- Polyuria, polydipsia, nocturia, 2ry nocturnal enuresis, polyphagia, loss of weight
- Weakness, lethargy & delayed wound healing
- Pyogenic skin infection & vaginal monilial infection
  - Diabetic ketoacidosis (DKA): (20-40% of diabetic children present with DKA)
    - Abdominal pain, vomiting, polyuria, fever
    - Clinical triad of dehydration, coma & acidotic breathing
    - Acetone odor of breath
    - Precipitating factors: infection, trauma, psychological disturbance
    - Mortality: 10%
    - **Laboratory diagnosis:**
      - ☑ Blood glucose  $> 300 \text{ mg/dL}$
      - ☑ Metabolic acidosis ( $\text{pH} < 7.3$ ,  $\text{HCO}_3^- < 16 \text{ mEq/L}$ )
      - ☑ Ketonemia, Ketonuria & glucosuria
    - **DD:**
      - Polyuria
      - Nocturnal enuresis
      - Acute abdomen (Medical & surgical causes)
      - Dehydration
      - RD
      - Encephalopathy
      - Stress hyperglycemia (No ketosis)
      - Starvation ketosis (No hyperglycemia)

**False results of HbA1c:**

1. Blood loss
2. Abnormal  $\beta$ -chain (Thalassemia, Sickle)

**Investigations**

1. **Blood glucose:** (see diagnostic criteria)
2. **Glycosylated Hb (HbA1c):** It is formed by non-enzymatic linkage between glucose &  $\beta$ -chain of Hb. It gives an idea about the average blood glucose over the last 8-12 weeks (Long-term glycemic control)  
*Normal* < 6 %, *Good control* = 6-8 %, *Fair control* = 8-10 %, *Poor control*  $\geq$  10 %
3. **Urine:** Glucosuria (DD: isolated renal glucosuria, Fanconi )
4. **OGTT:** Not routine
5. **Insulin level & C-peptide:** Marked  $\downarrow\downarrow$  (may be normal initially & in honeymoon phase)
6. **Autoantibodies, HLA**
7. **Screening of autoimmune diseases:** Thyroid, adrenal insufficiency, celiac
8. **Ophthalmologic examination:** (in children >10 yrs within 3-5 yrs of the onset)  
Fundus  $\rightarrow$  Hemorrhage, exudates, vascular changes, vitreous Hge, retinal detachment  
Slit lamp  $\rightarrow$  Cataract
9. **Microalbuminuria:** (Urinary albumin excretion rate (AER) = 30-300 mg/day)
10. **Quantitative sensory testing (QST) & nerve conduction velocity (NCV)**

**Complications**

**A) Acute complications:**

- DKA & Hyperglycemic hyperosmolar-nonketotic coma (HHNC)
- Hypoglycemia
- Hyperosmolality: Brain edema, myocardial depression, pulmonary edema, renal failure
- Brain edema: Iatrogenic during treatment of DKA or HHNC
- Arrhythmias:  $\uparrow\uparrow$  K,  $\downarrow\downarrow$  K,  $\downarrow\downarrow$  Ca

**B) Long-term complications:**

- Growth retardation (Mauriac syndrome: Short stature & hepatomegaly) " $\downarrow\downarrow$  Insulin"
- Syndrome of limited joint mobility: tight waxy skin & FTT
- Microvascular (prolonged DM >10 yrs)
  - ☒ **Retinopathy:** Non-proliferative & proliferative diabetic retinopathy  
Leading cause of blindness  
Rx: Control of DM - Laser photocoagulation (Vitreotomy may be needed)
  - ☒ **Nephropathy:**  
Leading cause of ESRD  
Microalbuminuria (early finding) followed by proteinuria, HTN & gradual  $\downarrow\downarrow$  KFT  
Rx: Control of DM & HTN, Dietary protein restriction  
Angiotensin-converting enzyme (ACE) inhibitors; e.g., Captopril
  - ☒ **Neuropathy** (motor, sensory & autonomic)  
Loss of HR variability (Early finding of autonomic neuropathy)  
Rx: Control of DM - Aldose reductase inhibitors - Antioxidants - Carbamazepine
- Macrovascular
  - ☒ Coronary artery disease
  - ☒ Cerebrovascular disease
  - ☒ Peripheral vascular disease

Glucose  $\rightarrow$  Sorbitol  $\rightarrow$  Osmotic damage

**C) Complications of insulin therapy:**

- Lipodystrophy (atrophy & hypertrophy)
- Insulin allergy: local: erythema, pruritis  
Systemic: urticaria, angioedema
- Insulin resistance: Local tissue enzyme: Rx: addition of protease inhibitor to insulin  
Circulating Ab: Rx:  $\uparrow\uparrow$  insulin dose

# Management of DKA

## Aim of treatment

- Expansion of intravascular volume
- Correction of electrolyte & acid base status
- Initiation of insulin therapy

## Clinical assessment

- Conscious level & neurological signs
- Vital signs
- Hydration status (shock, degree of dehydration)
- Acidotic breathing (Rapid & deep)
- Urine output (bag not catheter)
- Infection, vomiting & hematemesis

## Prepare 2 IV lines & Order lab for

- Evidence Blood glucose
- Electrolytes (Na, K, Cl, Ca, Mg, P)
- Osmolality
- Serum  $\beta$  (OH) butyrate
- Corrected Na =  $\text{Na} + 1.6 \times (\text{BG} - 100) / 100$
- Blood gases
- BUN & creatinine
- Effective osmolality =  $2\text{Na} + \text{Glucose} / 18$
- Urine for ketones
- Sepsis screen for infection

## Effects of hyperosmolality:

1. Brain edema
2. Renal failure
3. Cellular disruption

## Complications of Rx of DKA:

1. Hypoglycemia
2. Hypokalemia
3. Brain edema

## With correction of blood glucose

- $\downarrow\downarrow$  Osmotic diuresis
- Rapid rehydration

## Rapid $\downarrow\downarrow$ of effective osmolality

- $\uparrow\uparrow$  Risk of brain edema

## Fluid & electrolyte therapy

### A) Shock therapy:

If the patient is shocked → Anti shock 10-20 ml/Kg (NS or Ringer L) over 30 min

### B) Deficit requirement: (according to the degree of dehydration)

	< 30 Kg (< 8 yrs)	> 30 Kg (> 8 yrs)
Mild dehydration	50 ml / Kg	30 ml / Kg
Moderate dehydration	100 ml / Kg	60 ml / Kg
Severe dehydration	150 ml / Kg	90 ml / Kg

### C) Maintenance requirement: (1500 ml / m<sup>2</sup> / day)

### D) Total working fluids (Shock + Deficit + Maintenance): given over 36 hrs

- 1/2 → over 12 hours (Shock therapy is subtracted from the 1st half)
- 1/2 → over the next 24 hours
- Maximum amount should not exceed 4 L/m<sup>2</sup> / day
- Type of fluid:
  - Blood glucose > 300 → NS
  - Blood glucose 250-300 → G 5%: NS 1:1 (If acidosis is corrected)
  - G 10%: NS 1:1 (If acidosis is not corrected)
- Correction of hyperglycemia occurs well before acidosis. Therefore, insulin is still needed to control FA release & acidosis. So, glucose must be added to allow further continuous insulin infusion
- Duration of fluid therapy: Continued till
  - a. Correction of dehydration & acidosis
  - b. Tolerance of oral intake (sips of H<sub>2</sub>O then soft diet)
- In severe hyperosmolality (>340), the total fluid is given over 48 hrs
- In severe hyperosmolality & high corrected Na, half NS is used after 1<sup>st</sup> 2 hrs

**E) Potassium**

Potassium is added if initial serum k is  $< 6$  mEq/L & the patient voids urine  
It is better to give K partly as phosphate ( $\uparrow\uparrow$  2,3 DPG, KCl  $\uparrow\uparrow$  acidosis)

Serum K (mEq/L)	pH $> 7.1$	pH $< 7.1$
5 - $< 6$	10 mEq/L	15 mEq/L
4 - 5	20 mEq/L	25 mEq/L
3 - 4	30 mEq/L	35 mEq/L
$< 3$	40 mEq/L	45 mEq/L

**F) Bicarbonate therapy (rarely needed)**

- a. pH  $< 7 \rightarrow 40$  mEq /  $m^2$   
b. pH  $< 6.9 \rightarrow 80$  mEq /  $m^2$

HCO<sub>3</sub> Therapy  $\uparrow\uparrow$  Risk of brain edema

**G) Phosphate**

If serum phosphate  $< 0.5$  mmol/L, add 30 mmol / L NaPO<sub>4</sub> over 8 hrs

**H) Magnesium**

If serum magnesium  $< 0.5$  mmol/L, add 30 mmol / L MgSO<sub>4</sub> over 8 hrs

**Insulin therapy**

- Prepare insulin infusion: 50 U regular insulin + 500 ml NS (1 ml = 0.1U) or (50 + 50)
- Flush the plastic tube with 50 ml
- Use infusion pump
- Rate: 0.1 U / Kg / hr (1 ml / kg / hr) without a bolus. When blood glucose decrease to  $< 300$  mg% half the dose
- Satisfactory  $\downarrow\downarrow$  in blood glucose: 10% of the initial BG to maximum of 100 mg/dL/hr
- If bl. glucose  $\downarrow\downarrow$  more rapidly  $\rightarrow$  half the rate of insulin infusion
- If bl. glucose does not  $\downarrow\downarrow$  over 2 hrs  $\rightarrow$  double the rate of insulin infusion
- In case of *hypernatremia* (corrected Na  $> 145$  mEq/L) prepare insulin as 1:1  
250 U regular insulin + 250 ml 1/2 NS (1 ml = 1U)
- Duration of insulin therapy: Continued till
  - a. Correction of dehydration & acidosis (pH  $> 7.2$  HCO<sub>3</sub>  $> 10$  mEq/L)
  - b. Tolerance of oral intake (No vomiting)
- Then shift to SC regular insulin (started 1/2 hr before D/C of IV insulin)
- Lifelong SC insulin should be 0.5-1 U/Kg/day, divided as:
  - 40% Intermediate insulin (1/2 before breakfast, 1/2 before dinner)
  - 60% Regular insulin (1/3 before each meal)

**Monitoring**

- Clinical status
- Signs of brain edema: Give mannitol...
- Blood glucose hourly, then every 2 hours (when SC insulin is started)
- Blood gases & electrolytes every 2 hrs (in the 1<sup>st</sup> 8 hrs), then every 4 hrs
- Na trend
  - a. Positive Na trend: Corrected Na  $\uparrow\uparrow$  by 1.6 mEq/L for every 100 mg%  $\downarrow\downarrow$  glucose
  - b. Negative Na trend: Corrected Na does not  $\uparrow\uparrow$  or even  $\downarrow\downarrow$  with  $\downarrow\downarrow$  glucose  
This indicates accumulation of free water with  $\uparrow\uparrow$  risk of brain edema  
Management: Slow the rate of IVF (given over 48 hrs)

## Long-Term Management

### Insulin therapy

- a. **Dose:** average 0.5-1 U/Kg/day according to pubertal status  
Children in the honeymoon phase require only 60-70% of the full replacement dose

- b. **Types of insulin:** (Recombinant DNA)

	Example	Onset	Peak	Duration
Short acting	Regular insulin ( <i>Actrapid 40, 100</i> )	1/2-1 hr	1-2 hr	6-8 hr
	Lispro & Aspart ( <i>Novorapid</i> )	Much rapid with short <i>tail effect</i>		
Intermediate acting	Isophane insulin (NPH) ( <i>Insulatard 40, 100</i> )	1-2 hr	10 hr	24 hr
Long acting	Ultralent ( <i>Insuman</i> )	7 hr	16 hr	36 hr
	Glargine insulin ( <i>Lantus</i> )	Flat 24-hr profile ( <i>once daily</i> )		

- c. **Regimen:** (Three-injection regimen is commonly used)

- 40 % Intermediate insulin (1/2 before breakfast, 1/2 before dinner)
- 60 % Regular insulin (1/3 before each meal)

Ideal regimen = **Basal-bolus regimen** "Glargine + Lispro / Aspart"

(More physiologic with better glycemic control & ↓↓ risk of hypoglycemia)

d. **Technique:**

- Insulin syringes with fine needles calibrated in units
- SC injection with 90° angle to the skin
- Change the site regularly to prevent local complications (lipodystrophy)
- Short acting insulin should be drawn first
- Proper storage of vials (Refrigerator)

e. **Monitoring of blood glucose:**

- Self-monitoring of blood glucose (SMBG): At least 3-4 times/ day using blood glucose strips (Visual or glucometer)
- Continuous glucose monitoring systems (CGMS): using SC sensor
- Glycosylated hemoglobin (HbA1c)

f. **Adjustment of dosage:**

- Adjustment of dosage is based on blood glucose readings (SMBG)
- Target glucose level = 100-140 mg%
- Any change should be in the range of 10-15% "Extra-dose"
- With infections: ↑↑ the dose of insulin to avoid DKA
- With exercise: ↓↓ the dose of insulin to avoid hypoglycemia

g. **Other methods:**

- Insulin pump: (Continuous SC insulin infusion)
  - Programmed "basal-bolus"
  - More physiologic with more flexibility in timing of meals & snacks
  - Single needle injection every 3 days
  - Disadvantages: improper dosage
- Inhaled insulin (still under trial ?? pulmonary fibrosis)
- Oral insulin (still under trial)
- Pancreas & islet transplantation
- Regeneration of islets

**Dietary management** (Essential component of management)

- Number of meals: 3 main meals (breakfast, lunch & dinner) and 2 snacks
- Special pamphlets are available
- CHO counting is widely used in many centers (Each point = 15 g = 0.5-1 U)
- There are few dietary restrictions (even sweets & simple sugars are not totally forbidden)
- Non-nutritive sweeteners: Saccharine (? Cancer UB), Aspartame [Avoid Sorbitol, why?]

	Requirements & Comments	
<b>Calories</b>	75-100 Cal/Kg/day CHO =55%, Fat =30%, Protein =15%	
<b>CHO</b>	Complex CHO are preferred (starch products) High fiber content (grain) Avoid simple sugars, sweets & carbonated beverages	
<b>Fats</b>	<b>Encourage</b>	<b>Avoid (restrict)</b>
	Fats of plant origin Margarine Vegetable oil Fish & chickens	Fats of animal origin Butter Animal oil Fatty meats
<b>Proteins</b>	High protein intake may contribute to diabetic nephropathy Lower end of normal range is preferred 15%	

**C) Exercise**

- Regular exercise ↑↑ insulin receptors. Vigorous exercises may precipitate DKA
- No form of exercise is contraindicated.
- Risk of hypoglycemia is ↓↓ by ↓↓ insulin dose & ↑↑ food intake prior to exercise

**D) Basic education & emotional support****Hypoglycemic Reactions****Etiology**

1. ↑↑ Insulin dose
2. ↑↑ Exercises (specially sustained exercises e.g., running)
3. ↓↓ Calories
4. Honeymoon phase (Transient ↓↓ insulin requirement)

**Clinical picture**

A) ↑↑ Catecholamines: Tachycardia, palpitation, pallor, sweating, tremors

B) Cerebral glucopenia: Headache, hunger, drowsiness, confusion, coma, convulsions

**Treatment** (Urgent)

1. CHO drinks
2. IV fluids
3. Glucagon
4. Search for a cause (adjust insulin dose)

**Brittle Diabetes****Definition**

Unexplained wide fluctuations in B.G. in spite of high dose insulin, often with recurrent DKA

**Etiology**

Psychological or psychiatric problems (eating disorders, dysfunctional family dynamics)

**Treatment** (Supportive)

## Somogyi Phenomenon Dawn Phenomenon

### Definition

Early morning hyperglycemia

### Classification

	Dawn Phenomenon	Somogyi Phenomenon (rare)
Manifestation	Early morning hyperglycemia (before breakfast)	
	Without preceding hypoglycemia	With preceding late night or early morning hypoglycemia
Pathogenesis	Overnight production of GH ↓↓ insulin level	Hypoglycemia → ↑↑ anti-insulin → hyperglycemia
Diagnosis	Continuous glucose monitoring systems (CGMS)	

## Nonketotic Hyperosmolar Coma

### Definition & Clinical picture

It is a syndrome characterized by:

1. Severe hyperglycemia > 600-800 mg %
2. Hyperosmolarity > 350 mOsm/Kg H<sub>2</sub>O
3. Severe dehydration (Osmotic diuresis)
4. Lactic acidosis
5. No or mild ketosis (residual insulin is *sufficient* to # Ketogenesis)
6. Neurological manifestations: disturbed conscious level, motor deficits (hemiplegia...), why?

Dehydration

Acidosis

Hyperosmolarity

### Etiology (Not peculiar to DM)

#### A) Disease states:

1. DM
2. Head trauma
3. Severe infection & dehydration

#### B) Iatrogenic:

1. Drugs: Catecholamines, diazoxide, steroids
2. Suprasellar surgery
3. TPN

### Treatment

#### A) Fluid & electrolyte therapy

Total working fluids (Shock + Deficit + Maintenance): given over 36 hrs

- 1/2 → over 12 hours (Shock therapy is subtracted from the 1st half)
- 1/2 → over the next 24 hours
- Type of fluid:

Blood glucose > 300 → NS (or 1/2 NS)

Blood glucose 250-300 → G 10 %: 1/2 NS 1:1

Rapid correction of dehydration

Slow correction of osmolarity

#### B) Insulin therapy

- Prepare insulin infusion: 50 U regular insulin + 500 ml NS (1 ml = 0.1U)
- Flush the plastic tube with 50 ml
- Use infusion pump
- Rate: 0.05 U/Kg/hr (0.5 ml/kg/hr) without a bolus. Start with the 2<sup>nd</sup> hour of IV fluid

#### C) Monitoring (as in DKA)



## Type 2 Diabetes Mellitus

### Definition

Diabetes mellitus caused by insulin resistance with progressive defect in insulin secretion

### Etiology & Pathogenesis

	Type 1 DM	Type 2 DM
Formerly called	IDDM or juvenile	NIDDM or adult-onset DM
Incidence	2:1000	Increasing (parallel to obesity epidemic) 30% of new DM cases
Age	7-15 yrs (any age)	Older age (rapidly ↑↑ in children)
Sex	Equal	♀ > ♂
Body weight	Usually thin	Usually obese
Onset	Rapid	Insidious
Cause	Insulin deficiency	Insulin resistance (some degree of failure of insulin secretion)
Pathology	Pancreatic β-cells damage	Various degrees of β-cells impairment
Pathogenesis	Autoimmune destruction of β-cells	No evidence of immune disturbance
Insulin level	↓↓ or absent endogenous insulin	Relative hyperinsulinemia (but lower than control subjects)
Genetic component		Stronger, polygenic (aggravated by environmental factors)
Concordance	30-50% in identical twins	Almost 100% in identical twins
Susceptibility	HLA linked (DR3, DR4...)	Not HLA linked
Auto-Ab	ICA, IAA, GADA	May be +ve
Associated diseases	Thyroiditis, Celiac, Addison	Obesity, dyslipidemia, HTN (Metabolic S)
DKA	30% at presentation	Infrequent (stress, infection)
Need to insulin	Necessary (to prevent DKA)	Occasional
Acanthosis nigricans	Absent	Present in the majority

### Prevention

1. Change dietary habits & ↑↑ physical activity
2. Screening of high-risk children (Obese with +ve family history of DM)

### Treatment

1. Nutritional education
2. Weight reduction
3. Metformin (↓↓ Hepatic glucose production). CI in renal & liver impairment (*Cidophage*)

Metabolic S  
= Insulin resistance S  
Insulin resistance  
Hyperinsulinemia  
Obesity  
Dyslipidemia  
HTN

## Impaired Glucose Tolerance

### Definition

It is metabolic state intermediate between normal glucose homeostasis & DM. It is not a disease but risk factor

**Diagnosis** Oral Glucose Tolerance Test (OGTT). See the table

### Treatment

Weight reduction  
Diagnosis & Rx of other risk factors

Indications of OGTT:

1. Glucosuria
2. Hyperglycemia (stress, steroid)
3. At-risk (obese & +ve family)

# Parathyroid Glands

## Calcium Homeostasis

### Sources

Milk, cheese, yogurt

$$\text{Corrected Ca} = \text{actual Ca} + 0.8 (4 - \text{albumin})$$

### Blood Calcium

A) **Non-diffusible (45%)**: Bound to albumin & globulin. It is physiologically inactive

B) **Diffusible**:

a. **Non-ionized (5%)**: Forming complexes with citrate, bicarbonate,  $\text{PO}_4$ ...

b. **Ionized (50%)**: It is the physiologically active form

Hypoalbuminemia (e.g., Nephrotic S)  $\rightarrow$   $\downarrow\downarrow$  Total Ca with normal ionized Ca (No tetany)

Hyperphosphatemia ( $\uparrow\uparrow \text{PO}_4$ ) (e.g., Renal failure)  $\rightarrow$   $\downarrow\downarrow$  Ionized Ca (tetany)

The product of Ca X P = constant [Solubility product]

### Hormonal Control of Ca & Phosphate metabolism

$$\downarrow\downarrow \text{Mg} \rightarrow \downarrow\downarrow \text{PTH release} + \uparrow\uparrow \text{PTH resistance}$$

A) **Parathyroid hormone (PTH)**: " $\uparrow\uparrow$  Serum Ca level"

1. Intestine:  $\uparrow\uparrow$  Ca absorption indirectly through  $\uparrow\uparrow$  vitamin D

2. Kidney:  $\uparrow\uparrow$  Ca reabsorption,  $\uparrow\uparrow \text{PO}_4$  excretion &  $\uparrow\uparrow$   $1\alpha$  hydroxylase enzyme ( $\uparrow\uparrow$  Vit. D)

3. Bones:  $\uparrow\uparrow$  Ca mobilization from bones ( $\uparrow\uparrow$  Osteoclast number & activity)

B) **Vitamin D**: " $\uparrow\uparrow$  Serum Ca level"

1. Intestine:  $\uparrow\uparrow$  Ca absorption,  $\uparrow\uparrow \text{PO}_4$  absorption

2. Kidney:  $\uparrow\uparrow$  Ca reabsorption,  $\uparrow\uparrow \text{PO}_4$  reabsorption

3. Bones: Normal mineralization of bones. Excess vit. D  $\rightarrow$   $\uparrow\uparrow$  Ca mobilization from bones

C) **Calcitonin**: "Little effect on serum Ca level"

1. Produced by the parafollicular cells of the thyroid gland

2.  $\downarrow\downarrow$  Ca mobilization from bones ( $\downarrow\downarrow$  Osteoclast number & activity)

3. Important for fetal skeletal growth

D) **Thyroid hormones & GH**: " $\uparrow\uparrow$  serum Ca level"

E) **Glucocorticoids**: " $\downarrow\downarrow$  Serum Ca level"

Anti-vit. D effect ( $\downarrow\downarrow$  Ca intestinal absorption)  $\rightarrow$  Osteoporosis

### Normal blood Calcium

Total Ca = 9-11 mg/dL = 2.25-2.75 mmol/L = 4.5-5.5 mEq/L

Ionized Ca = 4.5-5.5 mg/dL = 1.1-1.3 mmol/L = 2.25-2.75 mEq/L

## Hypocalcemia

### Etiology

1. Hypoparathyroidism

2. Pseudohypoparathyroidism

3. Vitamin D deficiency: (See rickets)

4. Hypomagnesemia: Malabsorption (generalized & isolated)

$\uparrow\uparrow$  Renal loss (Hereditary AD, drugs; aminoglycosides, amphotericin B)

5. Hyperphosphatemia: CRF, tumor, phosphate therapy

a.  $\uparrow\uparrow$  Intake: Cow's milk, laxatives

b.  $\downarrow\downarrow$  Excretion: Renal failure

c. Transcellular shift: Tumor lysis S, rhabdomyolysis, acute hemolytic crisis

6. **Drugs**: Bisphosphonates, calcitonin...

7. **Others**: Acute pancreatitis, massive blood transfusion, citrated blood

### Causes of vitamin D deficiency:

1.  $\downarrow\downarrow$  Intake,  $\downarrow\downarrow$  Sun exposure

2.  $\downarrow\downarrow$  Absorption (Steatorrhea, anticonvulsant therapy)

3.  $\downarrow\downarrow$  Activation (Liver, renal)

4. Vit. D dependent rickets (type I, II)

# Hypoparathyroidism

## Definition

Deficient production of PTH or its action

## Etiology

### 1. Transient hypofunction:

- Early neonatal hypocalcemia: 12-72 hrs [Common in Preterm, IDM, Asphyxia]
- Late neonatal hypocalcemia: D3- D7 [Functional immaturity of the parathyroid glands]
- Transient idiopathic hypocalcemia: 1-8 weeks [Functional immaturity ...]

### 2. Maternal hyperparathyroidism (Mechanism: as in hypoglycemia of IDM)

Maternal hypercalcemia → Fetal hypercalcemia → Fetal ↓↓ PTH → Neonatal hypocalcemia

### 3. Aplasia of the parathyroid glands

- DiGeorge syndrome: Defect in development of 3<sup>rd</sup> & 4<sup>th</sup> pharyngeal pouches  
Aplasia of thymus & parathyroid glands [Hypocalcemia & immunodeficiency]  
Genetics: Microdeletion (22q)      Diagnosis: FISH  
C/P: Neonatal hypocalcemia, T cell deficiency (Viral, candida, chronic diarrhea, FTT)  
Facies: Fish mouth, Flat face, short Filtrum & hypertelorism  
Cardiac: Conotruncal anomalies (Interrupted aortic arch, truncus arteriosus)
- Other syndromes with 22q deletion: Velocardiofacial \$, Conotruncal-face \$, CATCH 22 \$ [Cardiac, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia]

### 4. XLR Hypoparathyroidism

### 5. AR Hypoparathyroidism

### 6. AD Hypoparathyroidism: Activation mutation of Ca sensing receptors

### 7. HDR syndrome: Hypoparathyroidism, Deafness & Renal anomalies

### 8. Immune

- Isolated
- Type I autoimmune polyendocrinopathy "HAM" (Hypoparathyroidism, Addison, mucocutaneous candidiasis)

### 9. Mitochondrial diseases

Kearns-Sayer syndrome (KSS)

### 10. Iatrogenic

Surgical removal during thyroidectomy

### 11. Idiopathic Hypoparathyroidism

### 12. Pseudohypoparathyroidism = Albright hereditary Osteodystrophy (End organ R.)

- Type IA: Defect in the PTH receptor  
Tetany + Skeletal + Mental retardation + BG calcification + Infertility (# TSH & GTH)
- Type IB: Defect in the adenyl-cyclase system
- Type II: Defect in the cell response to cAMP

## Diagnosis of PHP:

↓↓ Ca, ↑↑ PO<sub>4</sub>, ↑↑ Alkaline phosphatase, ↑↑ PTH

Response to exogenous PTH:

Exogenous PTH → ↑↑ Ca, ↓↓ PO<sub>4</sub>, ↑↑ cAMP (True hypo-)

Exogenous PTH → No ↑↑ cAMP (Type I)

Exogenous PTH → ↑↑ cAMP (Type II)



## Skeletal manifestations of PHP:

- Short stature
- Stocky build (Obesity)
- Short fingers (Brachydactyly) specially 3<sup>rd</sup> & 4<sup>th</sup>
- Index is longer than middle finger
- Exostosis & bowing

Pseudopseudohypoparathyroidism = C/P of PHP + Normal Ca & PO<sub>4</sub>

## Clinical picture

### (A) Tetany

#### a. Latent tetany: diagnosed by provocative tests

- ☒ *Chvostek's sign*: Tapping of the Facial nerve → Contraction of the facial muscles
- ☒ *Trousseau's sign*: Compression of the upper arm → Carpal spasm
- ☒ *Erb's sign*: Electrical stimulation with low Galvanic current → Muscle contraction
- ☒ *Peroneal sign*: Tapping of the peroneal nerve near the fibula → Pedal spasm

#### b. Manifest tetany

- ☒ Irritability & parasthesia
- ☒ Twitches & convulsions (Carpo-pedal spasm)
- ☒ Laryngismus stridulus
- ☒ Risus sardonius & trismus (Spasm of the facial muscles)

### (B) Ectodermal changes:

- a. Skin: Dry & rough
- b. Nail: Brittle with horizontal white lines
- c. Teeth: Hypoplastic
- d. Lens: Cataract

### (C) Picture of the cause: Addison, mucocutaneous candidiasis...

## Investigations

### ☒ Laboratory:

1. ↓↓ Ca (N = 9-11 mg/dL)
2. ↑↑ PO<sub>4</sub> (N = 3.5-6.5 mg/dL)
3. ↓↓ or normal alkaline phosphatase (N = 130-420 U/L)
4. ↓↓ PTH
5. Exogenous PTH → ↑↑ Ca, ↓↓ PO<sub>4</sub>, ↑↑ cAMP (blood & urine)

### ☒ Imaging:

- X-ray: ↓↓ Bone density
- ECG: Long QT interval
- EEG: Slow activity
- CT brain: Basal ganglia calcification

## Treatment

### (A) Emergency treatment of convulsions

- a. IV Calcium gluconate 10%: (1 cc/Kg) slowly
- b. IV Magnesium sulphate 10%: (1 cc/Kg)
- c. Oral calcitriol (1,25 dihydroxycholecalciferol)  
Initial dose: 0.25 µg/day  
Maintenance: 0.01-0.1 µg/Kg/day (max: 2 µg/day)

Monitoring of HR is essential  
Stop if bradycardia occurs

↓ Mg should be considered in any case  
of tetany not responding to IV Ca

### (B) Maintenance:

- a. Oral Calcium gluconate (Hi-Cal syrup)
- b. Dietary phosphate restriction: Milk, cheese, yogurt
- c. Oral calcitriol (1,25 Dihydroxycholecalciferol): 0.01-0.1 µg/Kg/day (Max = 2 µg/day)
- d. 1α hydroxycholecalciferol: 0.05-0.1 µg/Kg/day

# Hypercalcemia

## Etiology

### 1. PTH excess

- Primary hyperparathyroidism
- Tertiary hyperparathyroidism
- Ectopic PTH production "malignancy"
- Maternal Hypoparathyroidism

2ry hyperparathyroidism = Normal or  $\downarrow\downarrow$  Ca

### 2. Vitamin D excess

- Iatrogenic
- Sarcoidosis, TB, subcutaneous fat necrosis (inflammatory disorder of adipose tissue)

### 3. Excess Ca intake: Milk-alkali syndrome

### 4. Endocrinal causes: Thyrotoxicosis, Addison's disease

### 5. Malignancy: PTH-related peptide (PTHrP) secreting tumors (Paramalignant syndrome)

### 6. Drugs: Thiazides

### 7. Others:

- Prolonged immobilization
- Idiopathic hypercalcemia of infancy
- Williams syndrome

Genetics: Microdeletion (7q)

Diagnosis: FISH

C/P: Neonatal hypercalcemia, elfin facies (small mandible, upturned nose), mental retardation, supraaortic stenosis & social personality

### d. Familial hypocalciuric hypercalcemia: (AD with 100% penetrance)

-Inactivation mutation of Ca sensing receptors in the kidney & parathyroid gland

$\uparrow\uparrow$  Ca + normal or mildly  $\uparrow\uparrow$  PTH +  $\downarrow\downarrow$  urinary Ca/Creatinine ratio

C/P: usually asymptomatic discovered accidentally on routine investigations

### e. Hypophosphatasia

### f. Metaphyseal chondrodysplasia: activation mutation of PTH receptors

# Hyperparathyroidism

## Definition

Increased level of PTH

## Etiology

### (A) Primary Hyperparathyroidism " $\uparrow\uparrow$ PTH, $\uparrow\uparrow$ Ca"

- Adenoma
- MEN type I: Parathyroid (adenoma/hyperplasia), Pancreas, Pituitary
- MEN type IIA: Medullary carcinoma, Pheochromocytoma, Parathyroid
- Neonatal Hyperparathyroidism
- Transient Neonatal Hyperparathyroidism (2ry to Maternal hypoparathyroidism)  
Maternal hypocalcemia  $\rightarrow$  Fetal hypocalcemia  $\rightarrow$  Fetal  $\uparrow\uparrow$  PTH  $\rightarrow$  Transient neonatal hyperparathyroidism
- Familial hypocalciuric hypercalcemia

### (B) Secondary Hyperparathyroidism: (compensatory 2ry to hypocalcemia) " $\uparrow\uparrow$ PTH, $\downarrow\downarrow$ Ca"

- CRF
- Vitamin D deficiency

### (C) Tertiary Hyperparathyroidism " $\uparrow\uparrow$ PTH, $\uparrow\uparrow$ Ca"

It is autonomous parathyroid hyperplasia in longstanding 2ry hyperparathyroidism

### (D) Pseudohypoparathyroidism (PHP) " $\uparrow\uparrow$ PTH, $\downarrow\downarrow$ Ca"

## Clinical picture (of hypercalcemia)

- a. **Bones:** Weakness, bony pains, pathological fractures
- b. **Stones:** Renal stones, renal colics, hematuria, **polyuria**, polydipsia, renal failure
- c. **Abdominal groans:** Acute pancreatitis, anorexia, nausea, vomiting, constipation
- d. **Psychic moans:** Depression & psychosis,
- e. **Fatigue overtone:** Weakness
- f. **Parathyroid crisis** ( $\text{Ca} > 15 \text{ mg\%}$ ): Oliguria; renal failure, coma; convulsions

## Investigations

### ☒ **Laboratory:**

1.  $\uparrow\uparrow \text{Ca}$  ( $\text{N} = 9-11 \text{ mg/dL}$ )
2.  $\downarrow\downarrow \text{PO}_4$  ( $\text{N} = 3.5-6.5 \text{ mg/dL}$ )
3.  $\uparrow\uparrow$  or normal alkaline phosphatase ( $\text{N} = 130-420 \text{ U/L}$ )
4.  $\uparrow\uparrow \text{PTH}$  (done simultaneously with  $\text{Ca}$ )

**PTH is decreased in all cases of hypercalcemia except in:**

- Hyperparathyroidism
- Familial hypocalciuric hypercalcemia

### ☒ **Imaging:**

- X-ray: Subperiosteal bone erosion of phalanges, bone cysts (osteitis fibrosa cystica)
- ECG: short QT interval
- Abdominal US: Renal stones & nephrocalcinosis
- Neck US, CT, subtraction scintigraphy: for localization of parathyroid adenoma

## Treatment

1. Surgical exploration + intraoperative selective venous-sampling:
  - a. Adenoma: Removal
  - b. Hyperplasia: Total parathyroidectomy
2. Postoperative observation for the development of Hypoparathyroidism
3. Treatment of acute hypercalcemia:
  - a. Hydration (IV fluids)
  - b. IV bisphosphonate ( $\downarrow\downarrow$  Osteoclasts)
  - c. Steroids (prednisone): effective in hypercalcemia of sarcoidosis, vit. D intoxication, malignancy & SC fat necrosis [**not** in hyperparathyroidism]

## Endocrinology

1. A child aged 10 days has ambiguous genitalia. Which of the following is correct:

- a. Buccal smear shows chromatin negative
- b. Raised urinary 17-ketosteroids
- c. Genotype 45 XO would reliably explain the anomaly
- d. Klinefelter's syndrome is the most likely diagnosis
- e. Sex of rearing is strongly determined by the chromosomal sex

2. Which of the following doses of prednisolone is equivalent in its glucocorticoid potency to 20mg of hydrocortisone:

- 1. 2 mg
- 2. 5 mg
- 3. 10 mg
- 4. 15 mg
- 5. 20 mg

Dexamethasone is roughly 30 times more potent than hydrocortisone

3. A 15 year old girl is referred by her GP with agitation and weight gain. She has no past medical history of note. Her mother was treated for an 'overactive thyroid' and now she takes thyroxine tablets. Examination reveals no specific abnormalities with a BP of 112/70 mmHg.

Investigations reveal the following results:

- TSH 3.2 mU/L (0.35 - 5.0)
- Total T4 250 nmol/L (55 - 144)
- Free T4 12.9 pmol/L (9 - 24)
- Total T3 3.2 nmol/L (0.9 - 2.8)
- Free T3 3.8 pmol/L (3.0-5.8)

What is the most likely explanation for her condition:

- 1. Bulimia Nervosa
- 2. Dysthyroglobulinaemia
- 3. Factitious Thyrotoxicosis
- 4. Graves' Disease
- 5. Pregnancy

4. The thyroid hormone receptor is:

- 1. A gated ion channel
- 2. A cell surface receptor
- 3. A cytoplasmic protein.
- 4. A G-protein coupled receptor
- 5. A nuclear receptor

5. A 16 yr old ♀ patient is referred with 1ry amenorrhoea. Investigations reveal a 46XY karyotype. What is the most likely diagnosis:

1. Turner's syndrome
2. Maternal androgen administration during pregnancy
3. Noonan syndrome
4. Testicular feminisation syndrome
5. 5- $\alpha$ -reductase deficiency

6. 7 yr old ♂ who was operated upon for a craniopharyngioma, which of the following disorders can be expected over the next few years:

1. Diabetes mellitus
2. Hyponatraemia
3. Poor growth
4. Precocious puberty
5. Spastic diplegia

7. Which one of the following findings would not be expected in an 18 month old infant with poorly controlled hypothyroidism:

1. High plasma TSH concentration
2. Delayed bone age
3. Umbilical hernia
4. Diarrhea
5. Delayed development milestones

8. A 16 year old ♀ presents with hypertension and increasing weight. Which of the following features would be most suggestive of Cushing's syndrome rather than exogenous obesity:

1. Abdominal striae
2. Acanthosis Nigricans
3. Buffalo Hump (interscapular fat pad)
4. Moon face
5. Proximal myopathy

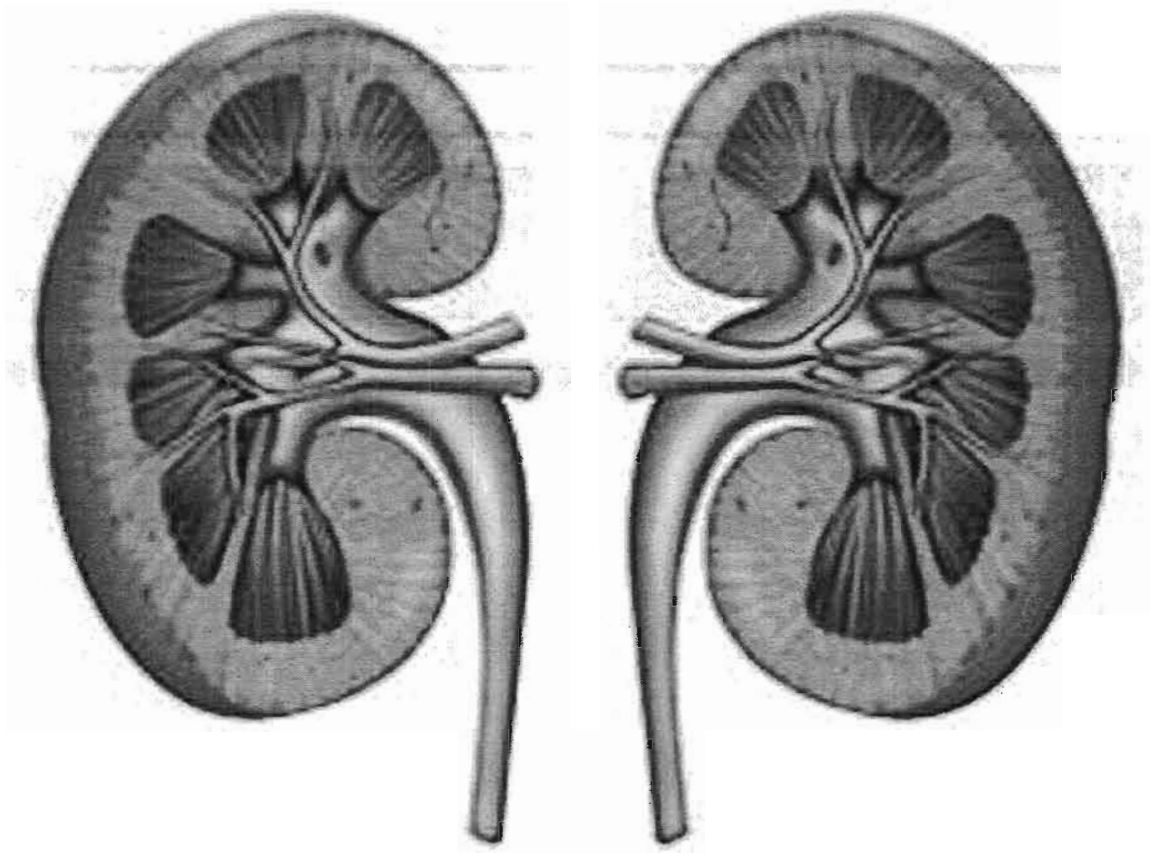
9. Which ONE of the following is true concerning ADH:

1. Its excess may cause hyponatremia
2. Ethanol potentiates its release
3. It is a steroid hormone
4. It acts on the proximal convoluted tubules
5. It is synthesized in the posterior pituitary



## Comprehension Questions

- [31.1] A 3650-g term infant has ambiguous genitalia, including an enlarged clitoris/microphallus and one palpable testis in the labioscrotal folds. Sonogram-reveals a uterus and ovaries. Which of the following is the most likely explanation for the child's ambiguous genitalia?
- A. Aromatase deficiency
  - B. Congenital adrenal hyperplasia
  - C. Female pseudohermaphroditism
  - D. Male pseudohermaphroditism
  - E. True hermaphroditism
- [31.2] A mother brings in her 1-week-old son who has vomited four times over the last 24 hours. He has no fever or diarrhea. The infant is breast-feeding poorly and is "floppy" per mom. He has had only one wet diaper in the last 12 hours. Physical examination reveals a lethargic infant who has lost 250g since birth, with pulse of 110 bpm, dry oral mucosa, and no skin turgor. Which of the following tests would be reasonable to consider after stabilization and electrolyte measurement?
- A. Serum cortisol level
  - B. Urine cortisol level
  - C. Serum 21-hydroxylase level
  - D. Serum 17 $\alpha$ -hydroxyprogesterone level
  - E. Serum testosterone level
- [31.3] A mother brings in her 15-year-old daughter because she has never started her periods. She otherwise is healthy and takes no medications. Her past medical history is unremarkable except for inguinal hernia repair as an infant. Family history is unremarkable. She is at the 75th percentile for height and weight, has Tanner stage IV breast development, and no pubic or axillary hair development. Her anogenital examination reveals a short, pocketlike vaginal opening. Which of the following is the most likely explanation for her amenorrhea?
- A. Adrenal tumor
  - B. Congenital adrenal hyperplasia
  - C. Pituitary tumor
  - D. Testicular feminization
  - E. Turner syndrome



# **Pediatric Nephrology**

**By**

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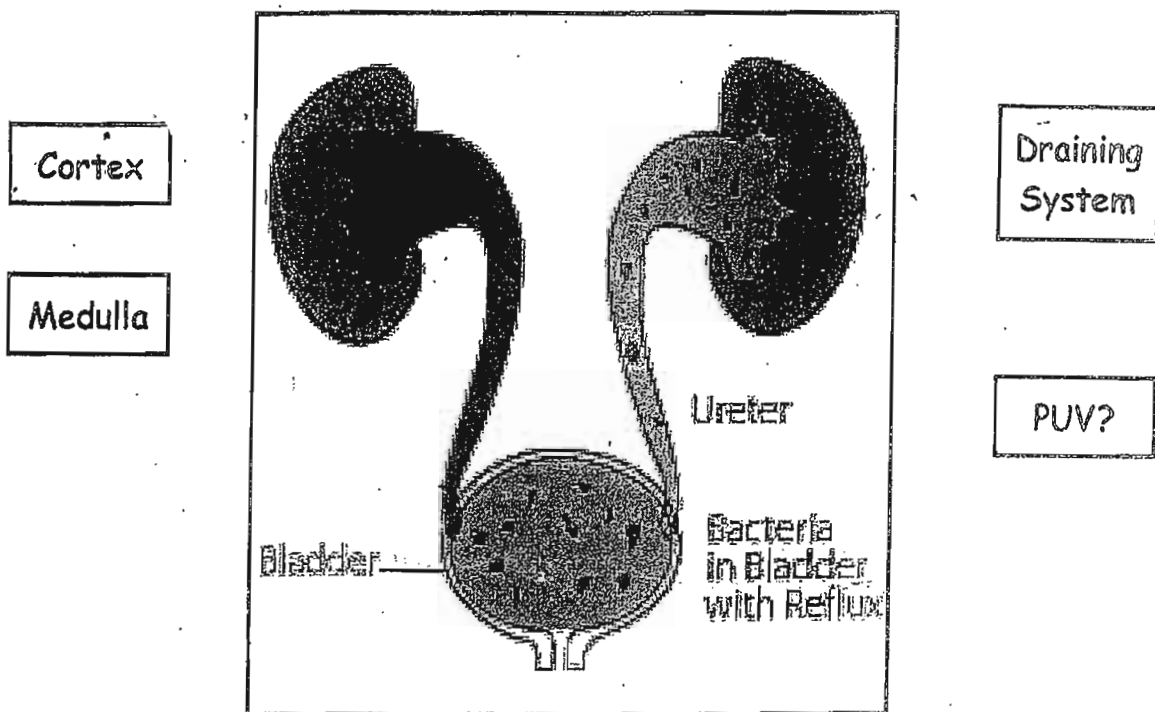
**2012**

# Introduction

## Functions of the Kidney

1. Regulation of fluid balance (Water homeostasis)
2. Regulation of electrolyte balance (Na, K, Ca, PO<sub>4</sub>)
3. Regulation of acid-base balance
4. Regulation of blood pressure
5. Excretion of waste products
6. Vitamin D activation
7. Stimulation of erythropoiesis (Erythropoietin)

## Anatomy



Kidney is formed of:

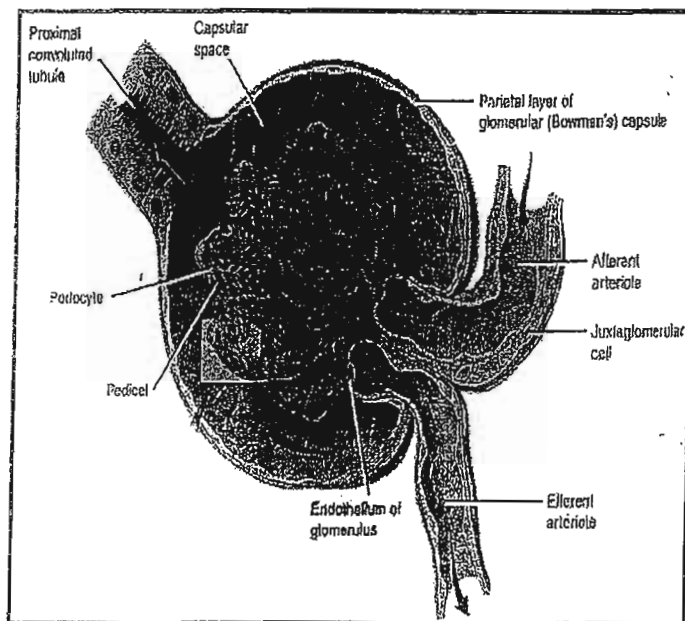
- Cortex (outer zone): Contains glomeruli, PCT, DCT & collecting ducts , PUV, etc.
- Medulla (inner zone): Contains loop of Henle, vasa recta & final portions of CDs  
It is formed of renal pyramids (renal papilla is the apex of renal pyramid)

Draining system for urine is formed of:

- Collecting ducts, Minor calyces, Major calyces, Renal pelvis
- Ureters: urine passes along the ureter by peristalsis. It passes obliquely for 2 cm in UB wall before opening
- Urinary bladder & Urethra

## Microanatomy

- Nephron = Glomerulus + Tubules
- Number of nephrons = 1 million / Kidney



Aff > eff

ACE inhibitors

**Nephron** is the functional & structural unit of the kidney. It is formed of:

- ☒ Glomerulus: formed of
  - Bowman's capsule: formed of visceral (Podocytes) & parietal layers of *Epithelium*
  - Tuft of 10-20 capillary loops supplied by *afferent arteriole* & drained by a slightly smaller efferent arteriole
  - Mesangium (= mesangial cells & mesangial matrix): lies between glomerular capillaries.  
It has supportive & immune functions
- ☒ Tubule: PCT, loop of Henle (thin & thick segments) & DCT

**Juxtaglomerular apparatus** is formed of:

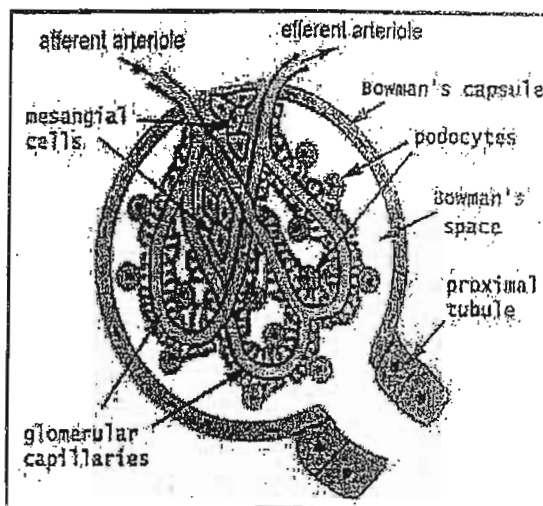
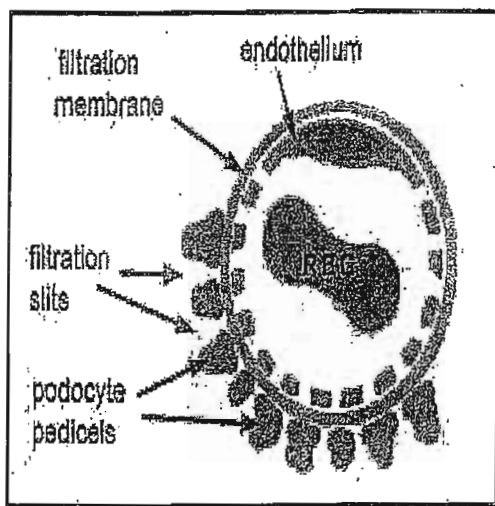
- Juxtaglomerular cells: in the wall of afferent arterioles (secrete renin)
- Macula densa cells: in the wall of DCT (stimulated by  $\downarrow\downarrow$  Na in the tubular fluid)
- Lacis cells: extra-glomerular mesangial cells of unknown function (in between)

**Filtration barrier** is formed of:

1. **Endothelial cells** of glomerular capillaries: fenestrated
2. **Capillary basement membrane**: formed of type IV collagen, proteoglycan...
3. **Epithelial cells** of the visceral layer of Bowman's capsule (= Podocytes): podocytes have foot processes which are implanted on the glomerular BM leaving filtration slits (covered by diaphragms)

**Filtration barrier** is effective in preventing proteinuria due to:

1. **Size-selective properties**: fenestrations prevent passage of high MW substances
2. **Charge-selective properties**: -ve charges that repel proteins



### Glomerular Filtration Rate

**Glomerular filtrate** = Plasma – macromolecules (proteins & lipids) [Sp. gravity = 1010]

**GFR** = amount of plasma filtered through glomeruli/unit time

**GFR** is the single best index of functioning renal mass

**GFR** reaches adult values by the age of 2-3 years

It can be estimated by calculating plasma clearance (Inulin or creatinine)

**GFR** is adjusted to standard surface area of  $1.73 \text{ m}^2$

Serum creatinine does not  $\uparrow\uparrow$  except when **GFR**  $\downarrow\downarrow$  to 50%

Serum **urea** is affected by protein intake

$$\frac{\text{Urine (mg/ml)} \times V \text{ (ml/min)}}{\text{Plasma (mg/ml)}}$$

#### Schwartz formula:

$$\text{GFR} = K \times \text{Height (cm)} / \text{serum creatinine}$$

*Convenient but not reliable*

#### K is variable according to the age & sex:

K = 0.33 (LBW infants < 1 year)

K = 0.45 (Term infant < 1 year)

K = 0.55 (Adolescent girls)

K = 0.75 (Adolescent boys)

	GFR (ml/min/1.73m <sup>2</sup> )
30 weeks GA	< 10
34 weeks GA	< 15
1 week (FT)	30
2 wks- 2 ms	60
2 ms- 2 years	90
2yrs-adults	130

# Investigations of Renal Diseases

## A) Laboratory

### ☒ Urine

#### ▫ Urinalysis

- **Physical:** Reaction (pH= 5-7), Specific gravity (1015-1025)
- **Chemical:** Proteins, Hb, bilirubin, glucose
- **Nitrites:** Only for screening (*False-positive & negative results*)
- **Leucocyte estrases**
- **Microscopic:**
  - RBC (< 5/ HPF)
  - Pus cells (< 5/ HPF)
  - Casts, (indicate **glomerular** disease) [Tamm-Horsfall ptn form their matrix]
    - Red cell casts (GN)
    - White cell casts (PN / GN)

- **Dysmorphic RBC:** Not reliable

#### ▫ Urinary Protein / Creatinine ratio



#### Protein/Creatinine ratio

- Normally < 0.2
- Proteinuria = 0.2-2
- Heavy range proteinuria > 2

#### ▫ Urine culture & sensitivity: $10^5$

#### ▫ Urinary Ca/Creatinine ratio (Normally < 0.2-0.8)

### ☒ Blood

- **KFTs:** serum creatinine & Urea (NB: Urea  $\approx$  2 x BUN)
- **Electrolytes:** Na, K, Cl, Mg
- **Ca, PO<sub>4</sub>, Alkaline phosphatase**
- **Albumin, total proteins & cholesterol**
- **Blood gases**
  - Acidosis in renal failure & RTA and
  - Alkalosis in Bartter syndrome)
- **CBC:**
  - Hb (Anemia in renal failure, HUS, SLE, Goodpasture)
  - RBC morphology (Fragmented in HUS)
  - PLT ( $\downarrow\downarrow$  in SLE, HUS, RVT)
  - WBC ( $\uparrow\uparrow$  in UTI,  $\downarrow\downarrow$  in SLE)
- **Others** (ASOT, ANA, Anti-ds DNA Ab, C<sub>3</sub>, C<sub>4</sub>, ESR...)

## B) Imaging

### 1. Micturating cystourethrogram (MCUG): [Invasive: Catheter]

- Vesico-ureteric reflux (VUR)
- PUV
- Neurogenic bladder

### 2. CT, MRI, MRU: Renal cysts & renal tumors

### 3. Renal ultrasonography

- **Size:** swollen in acute GN, small in CRF
- **Echogenicity:** (↑↑ in most renal diseases)
- **Cortico-medullary differentiation:** Lost or poor in CRF
- **Back pressure changes** (Hydroureter & hydronephrosis): Obstructive uropathy
- Non invasive
- Operator dependant

### 4. Renal scan

- DMSA: for detection of renal scar
- DTPA or MAG3: for estimation of renal function (Total & split)
- Indirect radionuclide cystography (IRC)

### 5. Intravenous pyelography (IVP):

- ?? Used in **selected** cases
- When detailed anatomy of the calyces or ureters are required (Before surgery)

### 6. Plain X ray: Urolithiasis & nephrocalcinosis

## C) **Invasive** (Renal biopsy)

3

1. L/M: Proliferation, crescent formation
2. I/F: Ig & Complement
3. E/M: GBM

## Posterior Urethral Valve

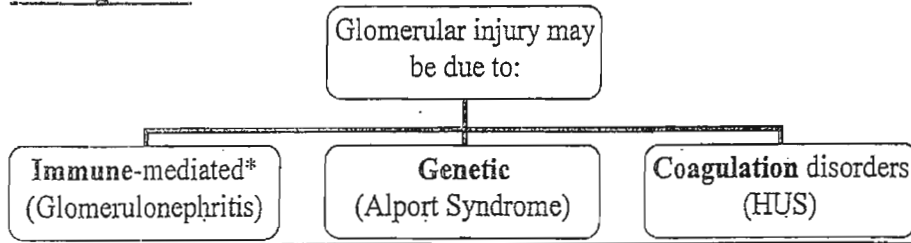
### Posterior Urethral Valve (PUV)

- **Commonest** cause of obstructive uropathy
- Mucosal folds in the posterior urethra
- Only in males
- **Presentation:** Antenatal hydronephrosis  
Interrupted urine stream  
Urine retention  
UTI
- **Effect:** UB hypertrophy  
Secondary VUR + UTI
- **Diagnosis:** Micturating cystourethrogram (MCUG)
- **Prognosis:** CRF may develop
- **Rx:** Cystoscopy (Valve resection)



# Glomerular Diseases

## Pathogenesis



## Glomerulonephritis

### Definition

Glomerular disease due to **immune** mechanism

### Etiology

1. Deposition of Ag-Ab complex in the glomeruli
2. Auto-Ab against glomerular antigens (Anti-glomerular basement membrane = anti-GBM)

**Mechanism of glomerular injury** [Activation of mediator pathways] → Inflammation

1. Complement system (Classic & alternative pathways)
2. Coagulation system stimulated by:
3. Kinin system (stimulated by coagulation system)

**Regardless the primary etiology,**  
the glomerulus has only **limited**  
number of histopathologic responses

### Pathology of glomerular injury

#### 1. Proliferation

Distribution:

- Generalized (involving all glomeruli) or Focal (involving only some glomeruli)
- Diffuse (all parts of the glomerulus) or Segmental (only some parts of the glomerulus)

Location:

- a. Endothelial cells: APSGN, MPGN, HUS, class III, IV lupus nephritis
- b. Epithelial cells: Membranous glomerulopathy, class V lupus nephritis
- c. Mesangium: IgA nephropathy, class II lupus nephritis

2. **Crescent** formation: proliferation of parietal epithelial cells + fibrin "Cellular" crescents  
Subsequent invasion with connective tissue "Fibroepithelial" & "Fibrous" crescents, Then?

#### 3. GBM thickening

- True ↑↑ thickness of GBM
- Subendothelial deposition of mesangial matrix & cells

#### 4. Sclerosis: Scar tissue within the glomerulus

#### 5. Tubulointerstitial fibrosis

### Note:

Clinical presentations	Pathologic types	Etiological classification
Nephrotic syndrome	MCNS	
Nephritic syndrome	FSGS	
Urinary abnormalities	MPGN	
Rapidly progressive GN	Membranous glomerulopathy	
ARF	Diffuse proliferative GN	
CRF	Mesangiocapillary GN	
	Crescentic GN	



# Hematuria

## Definition

Microscopic hematuria > 5 RBCs/ HPF in 10 ml freshly voided centrifuged urine

Persistent microscopic hematuria > 5 RBCs/ HPF on 3 separate UA done monthly

Hematuria may be:

- Microscopic or gross (macroscopic- visible by naked eye)
- Transient or persistent
- Initial, terminal or throughout the urine stream
- Painless or painful
- Asymptomatic or with other clinical features

### Red-brown urine (without RBCs):

1. Hb (acute hemolytic crisis)
2. Myoglobin (muscle injury, GSD...)
3. Drugs: rifampicin, nitrofurantoin
4. Dyes: berries, beets...
5. Metabolic errors: Melanin, porphyria, homogentisic acid (Alkaptonuria)

## Etiology

### 1. Glomerular (Renal or multisystemic diseases)

- Post infectious GN\* (APSGN)
- IgA nephropathy\*, Alport syndrome, Thin BM disease\*
- MPGN, Membranous glomerulopathy, FSGS
- SLE\*, HSP\*
- HUS
- RPGN
- Sickle cell glomerulopathy, HIV nephropathy
- Vasculitis: PAN, Wegener granulomatosis

### 2. Trauma\*

### 3. Tumors (Wilms tumor, leukemia, neuroblastoma)

### 4. Infection (UTI; Pyelonephritis & cystitis)\*; *Commonest cause*

### 5. Exercise

### 6. Hematologic: Bleeding tendency (ITP, hemophilia)

Hemoglobinopathy (Sickle cell anemia/ trait)

### 7. Hypercalcaemia, nephrocalcinosis & urolithiasis (stones)

### 8. Vascular: HUS, Renal vein thrombosis, vasculitis, nutcracker syndrome

### 9. Anatomic abnormalities:

- Cystic kidney disease (Polycystic kidney disease, MCDK)
- Obstructive uropathy (Hydronephrosis, PUJ obstruction)

### 10. Factitious syndrome / Factitious syndrome by-proxy (Munchausen)

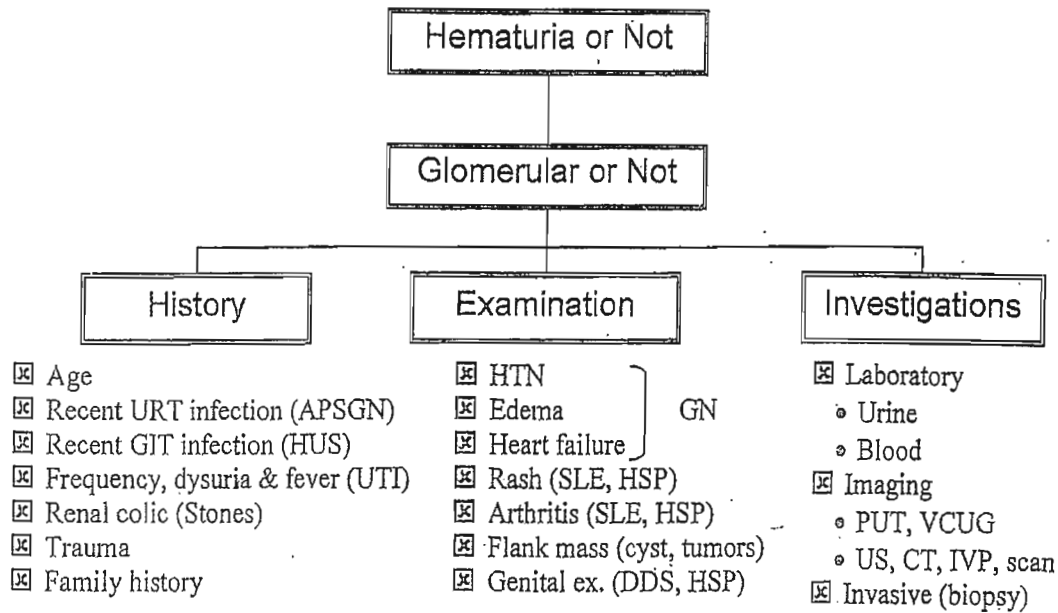
**Factitious syndrome (Munchausen):** adults falsify their own symptoms

**Factitious syndrome by-proxy (Munchausen by-proxy):** a parent, typically the mother, simulates or causes disease in a child

## Localization of hematuria

	Glomerular	Non-glomerular
Edema & HTN	May be present	No
Rash & Arthritis	May be present	No
Color	Brown, tea or cola-like, smoky	Bright red
Proteinuria	Often present	No
Dysmorphic RBCs	Yes	No
RBC casts	Yes	No

## Approach to a case of Hematuria



## Diseases commonly presenting as acute nephritic syndrome

1. Post infectious GN (APSGN)
2. IgA nephropathy
3. MPGN
4. SLE, HSP
5. HUS
6. Vasculitis: PAN, Wegener granulomatosis

### Hereditary Causes of Hematuria

1. IgA nephropathy, Alport syndrome, TBMD
2. SLE
3. Polycystic kidney disease
4. Sickle cell glomerulopathy
5. Urolithiasis

### Causes of Gross Hematuria

1. UTI\*\*
2. Trauma, Tumor
3. Hematological, Hypercalcuria
4. Meatal stenosis, perineal irritation
5. Glomerular
  - Post infectious GN (APSGN)
  - IgA nephropathy, Alport syndrome, TBMD
  - SLE, HSP

### Remember

1. The most common cause of gross hematuria is UTI
2. Nutcracker syndrome: Meso-aortic compression of Lt renal vein
  - Hematuria, proteinuria
  - Orthostatic hypotension
3. Asymptomatic isolated hematuria that persists on  $\geq 3$  UA over  $\geq 2$ -wk period should be investigated : Urine C & S, Ca/Cr, US, Electrolyte, KFTs

## Hypocomplementemic Hematuria??

## **Isolated Glomerular Diseases with Recurrent Gross Hematuria**

### **General Features**

1. **Sudden onset of gross hematuria:** Brown, tea or cola-like, smoky
2. **Short latent period:** 1-2 days after upper viral respiratory infection
3. **Spontaneous resolution of gross hematuria:** within 5 days
4. **Recurrence of the condition:** with another respiratory infection
5. **Routine investigations:** are non-conclusive
6. **Renal biopsy:** is the only diagnostic tool
7. **They may also present with:** microscopic hematuria &/or proteinuria

1. IgA Nephropathy
2. Alport Syndrome
3. Thin Glomerular BM disease

## **IgA Nephropathy**

(Berger Nephropathy)

### **Definition**

It is the most common chronic glomerular disease characterized by mesangial deposition of IgA as the only or the predominant Ig without evident of systemic involvement (SLE, HSP...)

### **Etiology**

Immune complex disease (?Genetic factors)

### **Pathology**

- ☒ **L/M:** Mesangial proliferation (↑↑ Mesangial cells + ↑↑ Mesangial matrix)
- ☒ **I/F:** Mesangial deposition of IgA as the only or the predominant Ig
- ☒ **E/M:** Mesangial deposits

### **Clinical picture** (Variable presentations)

- Recurrent gross Hematuria (*General features*)
- Microscopic hematuria &/or proteinuria
- Nephritic, Nephrotic or combined

### **Investigations**

#### **A) Laboratory**

- Urinalysis: hematuria (± proteinuria)
- KFT: may be ↑↑ in 20% of patients (20 yrs after the onset)
- IgA: No diagnostic value (↑↑ in only 15% of patients)
- Normal C<sub>3</sub> (DD: APSGN)

#### **B) Imaging:** Renal U/S

#### **C) Invasive:** Renal biopsy

### **Prognosis**

- Good prognosis in the majority
- Progressive renal disease in 20% of patients (20 yrs after the onset)

### **Treatment** [No specific therapy]

- Proper BP control
- ACE inhibitors ± Angiotensin II receptor antagonists
- Fish oil (Omega-3 polyunsaturated FA)
- Steroids & other immunosuppressives may be beneficial in some patients
- Tonsillectomy
- Renal replacement therapy (Dialysis or transplantation) in cases with ESRD

# Alport Syndrome

## Definition

It is the most common hereditary nephritis

## Etiology

Genetic disease caused by mutation in the genes coding for type IV collagen

	Mode of Inheritance	%	Gene	Protein coded
1	XL	85	COL4A5	$\alpha$ 5 chain of type IV collagen
2	AR	10	COL4A3	$\alpha$ 3 chain of type IV collagen
			COL4A4	$\alpha$ 4 chain of type IV collagen
3	AD	5	Linked	-

## Pathology

☒ L/M: Early

Early: No changes

Later: Mesangial proliferation ( $\uparrow\uparrow$  mesangial cells +  $\uparrow\uparrow$  mesangial matrix)

Glomerular sclerosis & tubular atrophy

☒ I/F: - ve

☒ E/M: Thickening, Thinning, Splitting & Layering of GBM

## Clinical picture

### A) Renal

- Recurrent gross hematuria (*General features*)
- Microscopic hematuria &/or proteinuria (more in ♂)
- Nephrotic syndrome (more in ♂)

### B) Extrarenal

- Sensorineural deafness: 90% of hemizygous ♂, 10% of heterozygous ♀, 67% of AR cases
- Ocular signs: anterior lenticonus (*Pathognomonic*), corneal erosions & macular flecks
- Platelet abnormalities (*Giant platelets*)

## Investigations

### A) Laboratory

- Urinalysis: Hematuria ( $\pm$  proteinuria)
- KFT: may be  $\uparrow\uparrow$  with the development of CRF
- Genetic analysis & antenatal diagnosis

### B) Imaging

- Renal U/S
- Audiogram: Defect starts in the high frequency range

### C) Invasive: Renal biopsy

## Prognosis

- ESRD occurs in 75% of ♂ before the age of 30 yrs
- ESRD occurs in 30% of ♀ by the age of 60 yrs

## Treatment [No specific therapy]

- Proper BP control
- ACE inhibitors (Captopril) may  $\downarrow\downarrow$  the rate of renal progression
- Renal replacement therapy (Dialysis or transplantation) in cases with ESRD

## Thin Basement Membrane disease

### Etiology

Sporadic or AD (COL4A3 & COL4A3)

### Pathology

- ☒ L/M: No changes
- ☒ I/F: -Ve
- ☒ E/M: Thinning of the GBM

### Clinical picture (Benign familial hematuria)

- Microscopic hematuria (Intermittent or persistent)
- Recurrent gross hematuria (*particularly after a respiratory illness*)

### Investigations

#### A) Laboratory

- Urinalysis: Hematuria (No proteinuria)
- KFT: normal

#### B) Imaging: Renal U/S

#### C) Invasive: Renal biopsy (E/M)

**Prognosis** Good (Rare cases develop proteinuria, HTN, renal insufficiency)

**Treatment** Follow up

## Idiopathic Hypercalciuria

### Etiology

AD

### Pathogenesis

- ☒ ↑↑ GIT Ca absorption
- ☒ ↑↑ Renal Ca excretion

### Clinical picture (Benign familial hematuria)

- Microscopic hematuria (usually persistent)
- Recurrent gross hematuria
- Dysuria
- Nephrolithiasis (15%)

### Investigations

#### A) Laboratory

- Urinalysis: Hematuria + ↑↑ Ca / Creatinine ratio > 0.2-0.8
- 24 hour urinary Ca > 4 mg/Kg
- KFT: normal

#### B) Imaging: Renal U/S

### Treatment

- Hydrochlorothiazide: 1-2 mg/kg/day ↓↓ renal Ca excretion
- Potassium citrate
- ↓↓ Dietary Na intake
- ↓↓ Dietary Ca intake is NOT recommended

### **Causes of Hypercalciuria:**

#### A) Hypercalcemia (↑↑ Ca)

- PTH excess
- Vit. D excess (sarcoidosis)
- Ca intake excess
- Endocrinal
- Malignancy
- Drugs (thiazides)
- Others: Williams  
Immobilization  
Familial

#### B) Hypercalciuria (Normal Ca)

- Idiopathic hypercalciuria
- RTA
- Metabolic acidosis
- Steroids
- Furosemide
- Bartter
- Ca intake excess
- Na intake excess
- Dent disease
- PG E<sub>2</sub>

# Post-Infectious GN

### Etiology

1. Acute post-streptococcal GN (APSGN)
2. Bacterial endocarditis (Strept. Viridans\*, Staph. aureus)
3. Infected ventricular shunts "Shunt nephritis" (Staph. epidermidis)
4. Parasitic infection (Malaria, Shistosomiasis, Leishmaniasis)

Immune complex deposition  
↓  
Glomerular injury (GN)

## Acute Post-Streptococcal GN

### Definition

It is the most common cause of acute nephritis in children

### Etiology

- It is an immune-mediated process following infection with "Nephritogenic strains" of group A  $\beta$ -hemolytic streptococci (12, 49) after a latent period of 1-3 weeks

Site of infection: Throat (pharyngitis) or Skin (impetigo)

- Streptococcal nephritogenic antigens:

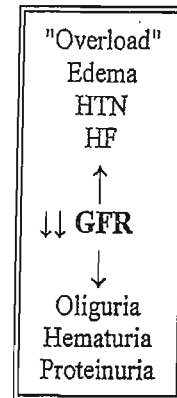
- a. Streptococcal pyogenic exotoxin (SPE B)
- b. Nephritis-associated streptococcal plasmin receptor

### Pathogenesis (Mechanism of renal injury)

1. Immune complex deposition (from the circulation or In-situ formation)
2. Molecular mimicry between Streptococci & glomerular antigens

All these factors lead to renal damage through:

- Activation of complement system (alternative pathway\*)
- Activation of coagulation cascade
- Activation of Kinin system
- Cytokine production & Free oxygen radicals



### Pathology (Diffuse proliferative GN)

- ☑ L/M: Proliferation of
  - Endothelial cells (Occlusion of capillaries)
  - Epithelial cells (Crescent formation in severe cases)
  - Mesangium ( $\uparrow\uparrow$  Mesangial matrix +  $\uparrow\uparrow$  Mesangial cells)
- ☑ I/F: Deposits of Ig & complement
- ☑ E/M: Deposits are subepithelial (under podocytes)

### Signs of volume overload:

1. Puffiness of the face (edema)
2. Congested neck veins
3. HTN
4. HF
5. Bilateral basal crepitations
6. Hepatomegaly
7.  $\uparrow\uparrow$  Weight ( $>$  Dry weight)

### Clinical picture (Peak incidence = 5 -12 years)

- Nephritic syndrome: acute onset of hematuria, oliguria, edema, hypertension & azotemia
  - Hematuria: gross painless, brown, tea or cola-like, smoky
  - Oliganuria: due to  $\downarrow\downarrow$  GFR
  - Edema: usually "mild" due to salt & water retention
  - Hypertension ( $\pm$  HTN encephalopathy): due to salt & water retention
- Hypertensive encephalopathy (Headache, vomiting, visual, ataxia, coma, convulsions)
- Volume overload??

### Complications

- ☑ HTN encephalopathy
- ☑ Heart failure
- ☑ Renal impairment: usually transient but may progress to RPGN; acidosis & electrolyte disturbance (Hyoerkalemia)

## Investigations

### A) Laboratory

- Urinalysis:

Color (brown, tea or cola-like, smoky)

↑↑ Specific gravity (1015-1025)

Hematuria & Pyuria (> 5/HPF)

Dysmorphic RBCs

Proteinuria (mild to moderate)

Casts (Hyaline, granular & red cell casts)

- KFT: may be ↑↑

- ↓↓ Na (dilutional), ↑↑ K (↓↓ GFR), ↓↓ Ca, ↑↑ PO<sub>4</sub>

- ↑↑ ASOT & streptozyme test

- ↓↓ C<sub>3</sub> (returns to normal within 4-8 weeks), Normal C<sub>4</sub> (DD: SLE)

### B) Imaging:

- Renal U/S: swollen, echogenic & prominent renal pyramids (preserved C/M differentiation)

- CXR, ECG & Echocardiography

- MRI: Reversible posterior leukoencephalopathy

### C) Invasive: Renal biopsy (not routine); indicated in:

- a. Nephrotic range proteinuria

- b. Normal C<sub>3</sub>

- c. Prolonged hypocomplementemia > 3 ms

- d. Prolonged gross hematuria or proteinuria > 3-6 ms

- e. RPGN or persistent renal dysfunction > 2 weeks

Renal biopsy is rarely indicated

## Prevention

Even early Rx of streptococcal infection (throat or skin) does not ↓↓ risk of APSGN

## Treatment

1. Hospital admission [Oliganuria, HTN, uremia, complications]

2. Observation: Vital signs, signs of overload?, ECG (T-wave for hyperkalemia)...

3. Penicillin (10 days) for eradication of infection & prevention of spread of nephritogenic strains to other

4. Diet: ↓↓ Na, K, protein

5. Fluid balance [Intake = insensible water loss + urine output]

6. Diuretics Furosemide 1-2 mg/Kg/day

7. Anti-hypertensives Ca channel blockers (Nifedipine) 0.5-3 mg/Kg/day

ACE inhibitors are not recommended (↓↓ GFR & ↑↑ K)

8. Rx of complications: Acidosis (NaHCO<sub>3</sub>), ↓↓ Na (fluid restriction) & ↑↑ K

**Hyperkalemia** is a medical emergency, with 3 primary goals of management:

☒ **Stabilizing the myocardial cell membrane** to prevent cardiac arrhythmia:

Calcium gluconate IV 1cc/Kg slowly

☒ **Shifting potassium intracellularly** "Transient effect"

Sodium bicarbonate IV

Regular insulin and glucose IV [Glucose: 0.5g/Kg + Insulin: 0.1 unit/Kg over 1 hour]

Inhaled or IV β-adrenergic agents (salbutamol)

☒ **Enhancing total body potassium elimination**

Sodium polystyrene sulfonate orally (Na Kayexalate) 1 g/Kg

Furosemide (Only if renal function is maintained)

Emergent HD (Peritoneal dialysis is not as efficient as HD in the Rx of ↑↑ K)

## Prognosis

- Complete recovery > 95% (6-8 wks)

- Recurrence is extremely rare

- CRF & mortality

# **Membranous Glomerulopathy**

## **Definition**

It is the most common cause of NS in adults accounting for only 5% of childhood NS

## **Etiology** (Immune complex disease)

### **A) Primary**

### **B) Secondary\*(80%)**

- Infections: HBV, malaria, Schistosomiasis
- Malignancy: lymphoma
- Immune: SLE\*
- Drugs: penicillamine

## **Pathology** (Membrane)

☒ L/M: Thickening of the GBM with spikes (Hair-comb appearance)

Minimal proliferative changes

☒ I/F: Deposits of Ig & complement

☒ E/M: Deposits are subepithelial (under podocytes)

## **Clinical picture** (2<sup>nd</sup> decade)

- Nephrotic syndrome
- Asymptomatic proteinuria
- Microscopic hematuria

## **Investigations**

### **A) Laboratory**

- Urinalysis: Hematuria (± proteinuria)
- KFT: may be ↑↑ with the development of CRF

### **B) Imaging: Renal U/S**

### **C) Invasive: Renal biopsy (Indicated in NS in a child > 10 yrs & persistent urinary abnormalities)**

## **Prognosis**

- Spontaneous remission in 40%
- Persistent proteinuria in 40%
- CRF in 20%

## **Treatment** [No specific therapy]

- Rx of the cause in 2ry membranous (may lead to remission)
- Salt restriction
- Diuretics
- ACE inhibitors (Captopril)
- Steroids + Chlorambucil (or Cyclophosphamide) may ↓↓ the rate of renal progression

# **Membranoproliferative GN**

(Mesangiocapillary GN)

## **Definition**

It is the most common cause of chronic GN in older children & young adults

## **Etiology**

### **A) Primary**

### **B) Secondary**

- Infections: HBV, malaria, Schistosomiasis
- Malignancy: lymphoma
- Immune: SLE
- Others: Lipodystrophy



**Pathology (Mesangiocapillary GN)**

	Type I (GN)	Type II (GN)	Type III (GN)
<b>L/M</b>	<ul style="list-style-type: none"> <li>Mesangial proliferation (<math>\uparrow\uparrow</math> cells + <math>\uparrow\uparrow</math> matrix)</li> <li>Thickening of the capillary wall with double-contour due to mesangial interposition <math>\rightarrow</math> <b>Tram-track</b> appearance</li> </ul>	Mesangial proliferation & capillary wall thickening as in type I but less prominent	Mesangial proliferation & capillary wall thickening as in type I but less prominent
<b>I/F</b>	Deposits of Ig & C <sub>3</sub> (subendothelial & mesangial)	Deposits of Ig & complement along GBM	Deposits of Ig & complement
<b>E/M</b>	Deposits are subendothelial & mesangial Intact GBM	GBM deposits (Intramembranous) <b>Dense deposit disease</b>	Deposits are subendothelial & subepithelial Disrupted GBM

**Clinical picture** (2<sup>nd</sup> decade)

- Nephrotic syndrome
- Nephritic syndrome (& RPGN)
- Asymptomatic proteinuria
- Microscopic hematuria

**Investigations****A) Laboratory**

- Urinalysis: Hematuria, proteinuria...
- KFT: may be  $\uparrow\uparrow$  with the development of CRF
- $\downarrow\downarrow$  C<sub>3</sub>
- C<sub>3</sub> Nephritic factor

**B) Imaging:** Renal U/S**C) Invasive:** Renal biopsy (Indicated in NS in a child > 10 yrs & persistent urinary abnormalities)**Prognosis**

- ESRD occurs in 50% of patients (10 yrs after the onset)
- Recurrence in the transplanted kidney (30-90%)

**Treatment** [No specific therapy]

- Long-term alternate-day prednisone therapy may  $\downarrow\downarrow$  the rate of renal progression

**Differential Diagnosis****APSGN**

	APSGN	MPGN
<b>Age</b>	$\downarrow\downarrow$	$\downarrow\downarrow$
<b>Gross Hematuria</b>	Present	
<b>Hypertension</b>	Present	
<b>C<sub>3</sub></b>	$\downarrow\downarrow$ (4-8 wks)	$\downarrow\downarrow$ (Persistent)
<b>Prognosis</b>	Good	50 % ESRD

**Hypocomplementemic nephritis**

	APSGN	MPGN	SLE
<b>C<sub>3</sub></b>	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow$
<b>C<sub>4</sub></b>	Normal	$\downarrow\downarrow$ or normal	$\downarrow\downarrow$

# Goodpasture Disease

## Definition

Goodpasture disease is characterized by:

- a. GN (Hematuria)
- b. Pulmonary hemorrhage (Hemoptysis)
- c. Antibodies against alveolar & GBM (Type IV collagen)

### Goodpasture syndrome:

GN & pulmonary hemorrhage that can be seen in several diseases (SLE, HSP...)

## Pathology (*Crescentic GN*)

- ☒ L/M: Crescentic GN (as in RPGN)
- ☒ I/F: Deposits of Ig
- ☒ E/M: Deposits are along GBM

## Clinical picture (Rare)

- Nephritic syndrome (RPGN)
- Hemoptysis

## Investigations

### A) Laboratory

- Urinalysis: Hematuria, proteinuria...
- KFT: ↑↑
- Normal C<sub>3</sub>
- Anti-GBM antibodies

### B) Imaging: Renal U/S

### C) Invasive: Renal biopsy

## Treatment [No controlled trials]

- Methylprednisolone & cyclophosphamide
- Plasmapheresis

## Prognosis (Bad)

- Pulmonary hemorrhage may be fatal
- Progression to ESRD is common

# **Rapidly Progressive (Crescentic) GN**

## **Definition**

It is glomerulonephritis characterized by:

- **Clinically:** Sudden progressive decline in renal function (over days to weeks)
- **Histological:** Crescents (proliferation of parietal epithelial cells of Bowman capsule + fibrin)

## **\*Etiology & Classification**

### **A) Immune mediated RPGN**

1. Post-infectious GN (APSGN)
2. MPGN
3. SLE
4. HSP
5. IgA nephropathy

### **B) Anti-GBM mediated RPGN**

1. Goodpasture disease
2. Idiopathic anti-GBM nephritis

### **C) ANCA mediated RPGN**

1. Microscopic polyangiitis
2. Wegener granulomatosis

### **D) Idiopathic RPGN**

## **\*Pathology**

- ☒ Crescentic GN (Crescents in > 50 % of all glomeruli)
- ☒ Picture of the cause is usually maintained

## **\*Clinical picture**

- Acute nephritic S: (acute onset of hematuria, oliguria, edema, hypertension & azotemia)
- ARF
- Picture of the cause (SLE, HSP...)

## **\*Investigations**

### **A) Laboratory**

- Urinalysis: hematuria ( $\pm$  proteinuria)
- KFT:  $\uparrow\uparrow$  with progressive renal impairment
- C<sub>3</sub>:  $\downarrow\downarrow$  in APSGN & SLE
- Anti-GBM antibodies
- Anti-neutrophil cytoplasmic antibodies (ANCA)
- Investigations of the cause

### **B) Imaging:** Renal U/S

### **C) Invasive:** Renal biopsy

## **\*Prognosis**

- RPGN 2ry to APSGN: Good prognosis
- Renal biopsy with  $\uparrow\uparrow$  number of fibrous crescents: Bad prognosis

## **\*Treatment**

- Supportive therapy (Diuretics, dialysis, HTN, hyperkalemia, seizures)
- Pulse therapy: Methylprednisolone (30 mg/Kg/dose) IV for 3 successive days followed by oral prednisone (2 mg/Kg/day) followed by gradual tapering (eod)
- AND Cyclophosphamide (500 mg/m<sup>2</sup>/dose) IV every month [Total = 6 doses]
- Plasmapheresis can be used in severe cases

## GN associated with SLE (Lupus Nephritis)

Renal affection is one of the most common feature of SLE & may be the only manifestation

WHO Class	Description	Pathology	I/F & E/M	Clinical Picture	Treatment
I	No histologic abnormalities			No clinical renal signs	No Rx
II	Mesangial lupus nephritis	Mesangial proliferation Mild = II-A Moderate = II-B	Mesangial deposits	Hematuria (microscopic) Proteinuria (mild) Normal renal function	Prednisone (1-2 mg/Kg/day) tid (till remission) followed by Slow tapering over 4-6 months
III	Focal segmental lupus nephritis	Focal & segmental mesangial proliferation Capillary wall necrosis, sclerosis, crescent formation	Mesangial & subendothelial deposits	Some as Class II Some as Class IV	Some as Class II Some as Class IV
IV 45%	Diffuse proliferative lupus nephritis (wire-loop GN)	All glomeruli show mesangial proliferation Capillary wall necrosis, sclerosis, crescent formation	Mesangial & subendothelial deposits	Hematuria Proteinuria (NS) Renal insufficiency	As class II + Cyclophosphamide IV (500 mg/m <sup>2</sup> /dose)/ month [6 doses] followed by IV/ 3 months [6 doses] Azathioprine & MMF may be used
V	Membranous glomerulopathy	Thickening of the GBM (spikes) Mild mesangial proliferation	Subepithelial deposits	Nephrotic \$	Steroids + Chlorambucil

Deposits = Ig & complement, Mesangial proliferation = ↑↑ cells + ↑↑ matrix, MMF = Mycophenolate Mofetil

**im of Rx** Induction of clinical & serologic remission

**Pulses of Methylprednisolone:**  
1. ↑↑ anti inflammatory effect  
2. ↓↓ steroid side effects

### activity & Chronicity indexes

Acute lesions		Chronic lesions	
Glomerular	Tubulointerstitial	Glomerular	Tubulointerstitial
Capillary hypercellularity Fibrinoid necrosis Cellular crescents Leukocyte infiltration	Mononuclear cell infiltration Tubular necrosis	Glomerular sclerosis Fibrous crescents Fibrous adhesions Extramembranous deposits	Interstitial fibrosis Tubular atrophy
Activity lesions are <b>potentially reversible</b> with Rx		Chronicity lesions are <b>irreversible</b> even with Rx	

**Deterioration of renal function in SLE:**  
1. Active lesion (↑↑ Rx)  
2. Sclerotic lesions  
3. Nephrotoxicity

**Prognosis** Aggressive immunosuppressive therapy improves the prognosis. Class IV has the worst prognosis

**Other lines of Rx** IVIG, plasmapheresis, Rituximab (Anti-CD 20 monoclonal Ab)

# Hemolytic Uremic Syndrome

## Definition:-

It is the most common cause of intrinsic ARF in children < 4 years. It is characterized by "triad" of MAHA, thrombocytopenia & uremia

## Classification

- A) D+ HUS\* (Preceded by diarrhea)  
 B) D- HUS (Not preceded by diarrhea)
- This classification is simple but not accurate

## Criteria of Diagnosis (CDC):-

Atypical HUS: No Diarrhea

- A) **Laboratory criteria:** Acute onset of MAHA + Renal affection  
 B) **Confirmed HUS:** Laboratory criteria + onset within 3 wks of acute diarrhea  
 C) **Probable HUS:**  
 - Laboratory criteria (+ No history of diarrhea in the preceding 3 wks)  
 - Laboratory criteria (Except MAHA) + History of diarrhea in the preceding 3 wks

## Etiology:-

### 1. Infection-induced

- Verotoxin-producing E. coli (O157:H7 is the commonest serotype)
- Shiga toxin-producing Shigella dysenteriae type 1
- Neuraminidase-producing Streptococcus pneumoniae: usually pneumonia & empyema
- HIV

### 2. Genetic

- Complement factor H deficiency
  - Complement factor I deficiency
  - Complement factor B deficiency
  - Membrane cofactor protein (MCP) deficiency (= CD46)
  - Familial AR type
  - Familial AD type
  - Sporadic recurrent type
  - Von-Willebrand factor-cleaving protease (ADAMTS 13) deficiency →
  - Vitamin B<sub>12</sub> metabolism defect
- homocysteine → vit B<sub>12</sub> → methionine

### 3. Disease-associated:-

- SLE, APS → Anti-phospholipid Ab
- BM transplantation
- Malignant hypertension
- HELLP syndrome: Hemolytic anemia, elevated liver enzymes, low platelet count

### 4. Drug-induced:-

- Calcineurin inhibitors (Cyclosporine, tacrolimus)
- OCPs

## Pathology (Vascular)

### L/M:

- Thickening of capillary walls, narrowing of the lumina, fibrin thrombi (in glomerular capillaries), thrombi (afferent arterioles & small arteries)
- Late: Glomerular sclerosis

I/F: - Ve maybe we get genetic causes related to complement factor defect

E/M: Mesangial & subendothelial deposition of amorphous material

## Pathogenesis (Endothelial cell damage)

- ☐ Diarrhea-associated HUS: Direct endothelial cell damage by Verotoxin or Shiga toxin
- ☐ Pneumococcal-associated HUS:  
Neuraminidase → Cleavage of sialic acid (on endothelial cell & RBC membrane) →  
Exposure of Thomsen-Friedenreich (T antigen) → IgM activation → Endothelial damage
- ☐ Disorders of complement regulation (FH, FI, MCP): ↑↑ Complement activation
- ☐ Deficiency of ADAMTS 13: ↑↑ Von-Willebrand factor → Platelet aggregation
- ☐ Vitamin B<sub>12</sub> metabolism defect: ↑↑ Homocysteine

## Clinical picture (Peak incidence = 6 ms - 4 years)

### A) HUS caused by VTEC

- The onset of HUS occurs a few days after GE (usually bloody stools) "as few as 3 days"
- Acute onset of pallor, oliguria, irritability, weakness & petechiae
- Dehydration or overload (Diarrhea & ARF)
- Can be relatively mild or severe complicated

### B) Pneumococcus-associated HUS

- Usually pneumonia & empyema

### C) Genetic HUS

- The onset is insidious
- Can be triggered by infection (GE or respiratory tract infection)
- Risk for recurrence
- Should be considered if there is no history of diarrhea or pneumococcal infection

## Complications

- ☒ HTN encephalopathy
- ☒ CNS: Irritability, seizures & coma
- ☒ Heart failure
- ☒ Extrarenal: Cardiac (Myocarditis, pericarditis, arrhythmias)  
GIT (Colitis, perforation, intussusception)  
Pancreatitis, IDDM
- ☒ ARF: Acidosis, Electrolyte disturbance
- ☒ Severe anemia
- ☒ Severe bleeding is rare?

## Investigations

### A) Laboratory

- Urinalysis (Mild abnormalities): Hematuria & pyuria (> 5/ HPF), mild p
- CBC
  - Hb (anemia)
  - Fragmented RBC (Helmet & burr cells) **MAHA**
  - Reticulocytosis
  - PLT (Thrombocytopenia 20.000-100.000)
  - WBC (leukocytosis > 20.000)
- KFT: ↑↑ (Serum creatinine > 1 mg/dL)
- ↓↓ Na (Dilutional)
- ↓↓ K (Paradoxical) *due to diarrhea*
- Bilirubin: may be ↑↑
- Coombs test: Negative *non-immune hemolytic anemia*
- PT & PTT: Normal
- Stool C&S (O157:H7)
- Serum Ab to E.coli O157:H7 antigen
- C<sub>3</sub> Normal (↓↓ in some genetic cases)

### B) Imaging: (Renal U/S, CXR, ECG & Echocardiography)

- Renal U/S: swollen, echogenic & prominent renal pyramids (preserved C/M differentiation)

### C) Invasive: Renal biopsy (Not routine); indicated in:

- × a. Patients who fail to develop thrombocytopenia
- b. Prolonged impairment of renal function > 2 weeks
- a - Absence of thrombocytopenia

**Renal biopsy is rarely indicated:**

1. The diagnosis is mainly clinical
2. Thrombocytopenia

### → Prevention

- Cooking meat at high enough temperature & hand washing
- Cautious prescription of antibiotics in VTEC colitis. Why?\*
- Oral Stx binding agents (Synsorb): Unsuccessful

### → Treatment

- 1. Hospital admission & Management of ARF
- 2. Close monitoring: Vital signs, signs of overload, electrolytes (ECG), complications...
- 3. Fluid balance [Intake = insensible water loss + urine output]
- 4. Packed RBCs to keep Hb > 7 g% *→ will be destroyed.*
- 5. Platelets transfusion is **not** indicated, why? *→ no evidence of bleeding*
- 6. Antibiotic Rx is **not** recommended in VTEC, why? But given in pneumococcal infection
- 7. Antihypertensives Ca channel blockers (Nifedipine) 0.5-3 mg/Kg/day & diuretics  
ACE inhibitors are not recommended (↓↓ GFR)
- 8. Sufficient calories: if severe vomiting, ondansetron. TPN can be used: as major attraction of G<sub>6</sub>P
- 9. **Early initiation of dialysis** (if anuria or significant oliguria develop): PD is preferred, but in patients with bowel gangrene or perforation, HD is indicated *→ associated with overload*
- 10. FFP or plasmapheresis: may be given in genetic cases (e.g., ↓↓ ADAMTS 13 & CFH)
- 11. **Specific replacement therapy**: in some of the genetic forms
- 12. Anticoagulants, thrombolytic therapy, steroids & anti-platelet: Ineffective

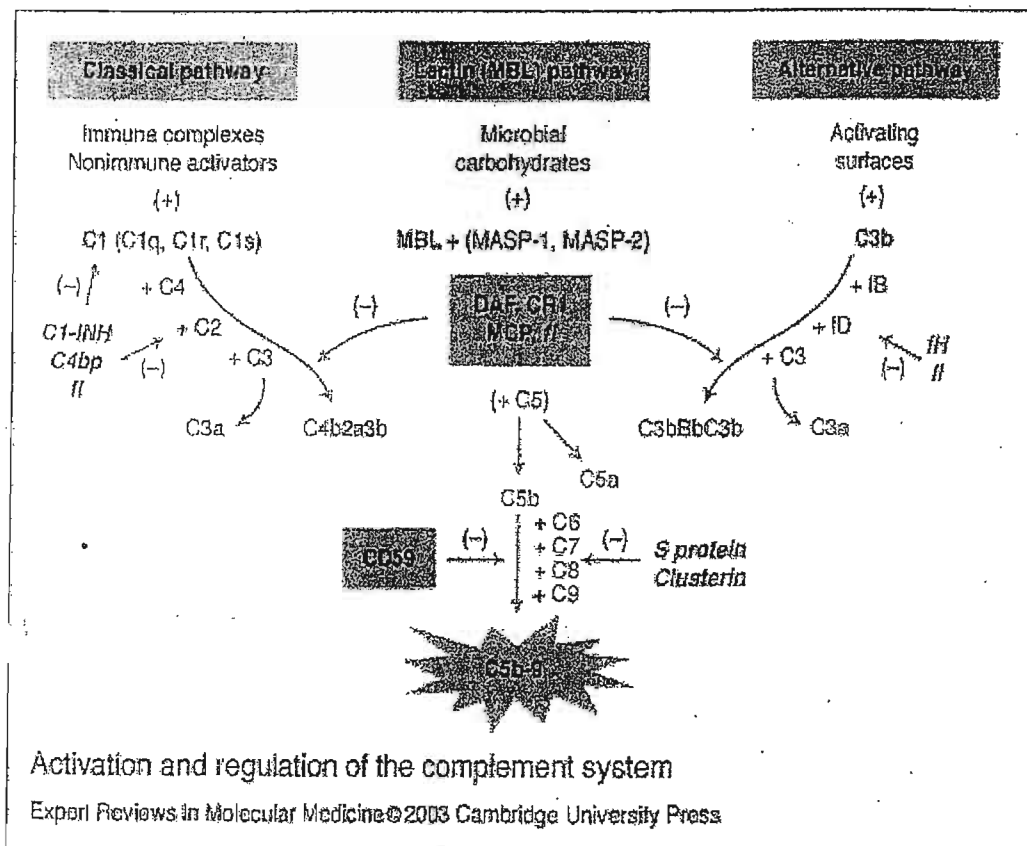
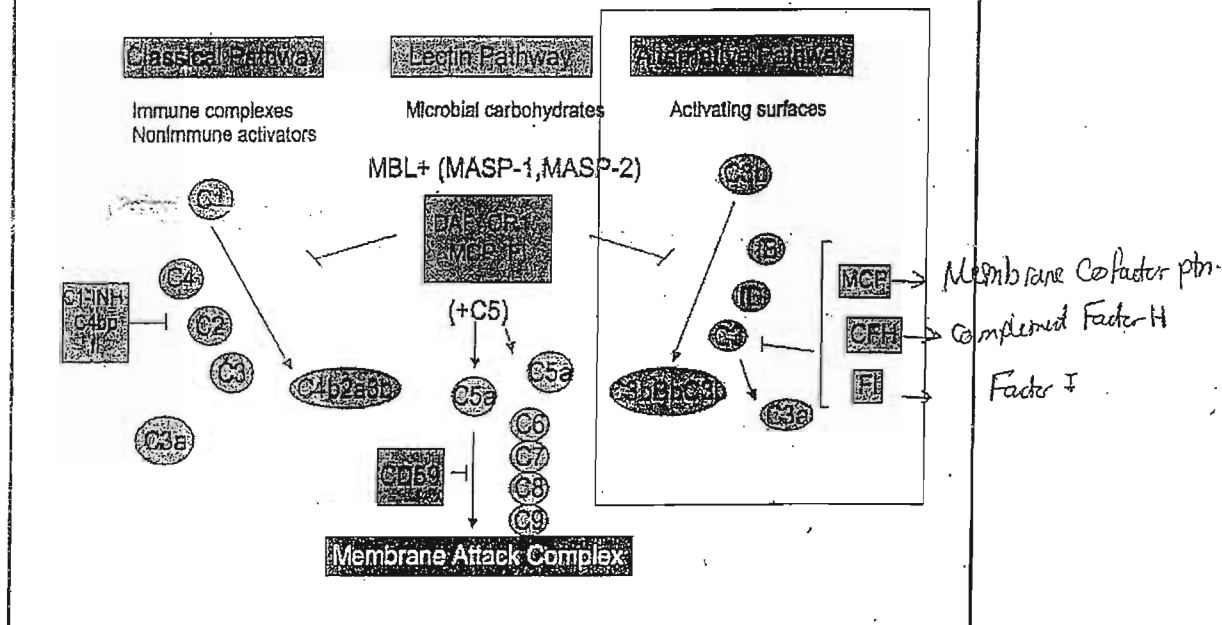
### → Prognosis

#### ■ Diarrhea-associated HUS:

- Mortality < 5%
- Most recover renal functions
- 20-30% develop CKD

#### ■ Other types of HUS: Poor prognosis

# The complement cascade



Activation and regulation of the complement system

Expert Reviews in Molecular Medicine © 2003 Cambridge University Press



# Renal Vein Thrombosis

## \* Definition

It is thrombosis of the renal vein. It is one of the causes of MAHA (hematology)

\* Etiology Cong + Acquired Thrombophilia from hematology

A) **Neonates & infants:** usually associated with asphyxia, sepsis, shock, dehydration, IDM

B) **Older children** (See Thrombophilia)

- Nephrotic syndrome (specially membranous glomerulopathy)
- Dehydration
- Congenital cyanotic heart diseases
- Hereditary predisposition to thrombosis (e.g., protein C & S deficiency...)
- IV contrast agents

## Pathogenesis (Virchow's triad)

1. Endothelial cell injury (asphyxia, sepsis, shock)
2. ↓↓ Blood flow (Sepsis, shock, dehydration, NS, polycythemia)
3. Hypercoagulable state (e.g., protein C & S deficiency...)

## \* Clinical picture

- Picture of the cause (Diarrhea) → HUS
- Flank pain
- Flank mass
- Hematuria, HTN
- ARF (in bilateral cases)

## \* Investigations

### A) Laboratory

- Urinalysis (mild abnormalities)
  - Hematuria (RBC > 5/HPF)
- CBC (MAHA)
  - Hb (anemia)
  - Fragmented RBC (Helmet & burr cells)
  - PLT (Thrombocytopenia 20,000-100,000)
- KFT: ↑↑ in bilateral cases

### B) Imaging:

- Renal U/S: Marked renal enlargement, echogenic & prominent renal pyramids (preserved C/M differentiation)
- Renal Doppler: detect blood flow

### C) Invasive: Contrast studies (should be avoided)

## Treatment

1. Correction of fluid & electrolyte imbalance (dehydration)
2. Management of ARF
3. Anticoagulants: Heparin
4. Thrombolytic agents: Streptokinase, urokinase or tissue plasminogen activator (rTPA)??
5. Surgical thrombectomy in IVC thrombosis

Controversial
---------------

## Prognosis

The involved kidney will undergo progressive atrophy & scarring → CRF & HTN

# \*Proteinuria\*

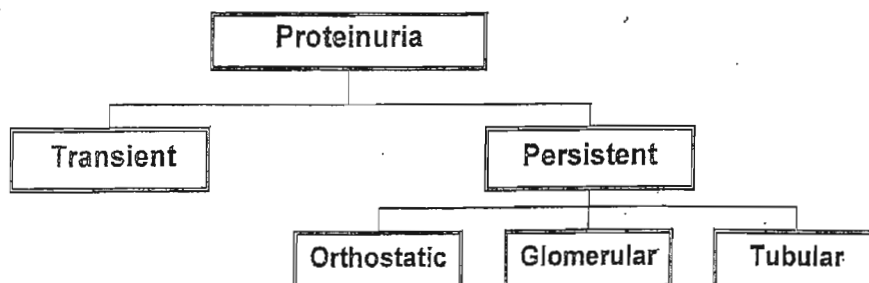
Def  
Classification  
Inv.  
Ind of renal biopsy  
Detection of proteinuria.

## Definition

- Proteinuria is excretion of abnormal amounts of protein in urine.
- Normal urinary protein excretion is  $\leq 4 \text{ mg/m}^2/\text{hr}$  or  $< 150 \text{ mg/day}$  or Pr/Cr ratio  $< 0.2$
- Heavy-range proteinuria: Urinary Pr/Cr ratio  $> 2$  or urinary protein excretion  $> 40 \text{ mg/m}^2/\text{hr}$ .
- 24-hr urine protein has largely been replaced by the spot Pr/C ratio
- Microalbuminuria: Urinary albumin excretion of 30-300mg/g creatinine  
↳ seen in diabetic pt

## Classification

- According to the duration:
  - ☒ **Transient:** Fever, HF, exercise, seizures, dehydration. Common on random UA (10%)
  - ☒ **Persistent (Fixed)**
- According to the associated symptoms:
  - ☒ Asymptomatic
  - ☒ Symptomatic: Edema, hypertension, hematuria, renal dysfunction
- According to the origin:
  - ☒ Glomerular
  - ☒ Tubular



	Glomerular proteinuria	Tubular proteinuria
<b>Mechanism</b>	$\uparrow\uparrow$ Glomerular capillary permeability	$\downarrow\downarrow$ Tubular protein reabsorption (mainly PCT) <del>off Function</del>
<b>Amount</b>	Variable up to 30 g/day	Usually $< 1 \text{ g/day}$
<b>Type (Urine ptn Electrophoresis)</b>	Selective (MCNS) or non-selective (others)	-
<b>Major proteins</b>	Albumin	LMW proteins (lysozyme, GH, $\beta_2$ -microglobulin) Not albumin
<b>Association</b>	• Hematuria, edema, hypoalbuminemia, HTN, renal dysfunction	• Picture of the cause (Fanconi, glucosuria, phosphaturia...)
<b>Etiology</b>	<ul style="list-style-type: none"> <li>• Idiopathic nephrotic syndrome (MCNS)</li> <li>• Post-infectious GN (APSGN)</li> <li>• IgA nephropathy, Alport syndrome</li> <li>• MPGN, membranous glomerulopathy</li> <li>• FSGS</li> <li>• SLE, HSP</li> <li>• HUS</li> <li>• RPGN</li> <li>• Sickle cell glomerulopathy</li> <li>• Amyloidosis</li> </ul>	<ul style="list-style-type: none"> <li>• Cystinosis, Lowe syndrome</li> <li>• Galactosemia, Tyrosinemia</li> <li>• Wilson</li> <li>• Dent disease (XLR nephrolithiasis)</li> <li>• Fanconi-Bickel syndrome</li> <li>• Heavy metals</li> <li>• TIN, ATN</li> <li>• Obstructive uropathy</li> <li>• VUR, Chronic pyelonephritis</li> <li>• Renal cystic diseases</li> </ul>

## ✓ ✓ ✓ ✓ ✓ Orthostatic (Postural) Proteinuria ✓

- Commonest cause of persistent proteinuria (60%)
- Proteinuria occurs in the upright position
- It decreases or disappears in the supine position
- Etiology: Altered renal hemodynamics (compression on the left renal vein)
- Diagnosis: supine & upright urine collection
- Proteinuria < 1 g/day, No hematuria, edema, hypoalbuminemia, HTN, renal dysfunction
- Prognosis: Benign condition (F/U is required)
- Treatment: Reassurance

✓ Investigations (see before: mention)

✓ Indications of Renal biopsy

Hematuria, HTN, Heavy range-proteinuria (Not MCNS), renal dysfunction

✓ Detection of proteinuria ✓

1. Urinalysis
2. Dipstick method
3. Urinary A/Cr ratio ( $N < 0.2$ )
4. 24 hr urine proteins (?? Collection)

24 hr urine protein has been largely replaced by the spot A/C ratio

# Nephrotic Syndrome

## Definition

It is a **Clinico-laboratory** syndrome characterized by:

1. Generalized edema
2. Heavy-ranged proteinuria: Urinary Pr / Cr ratio > 2 or protein excretion  $\geq 40 \text{ mg/m}^2/\text{hr}$
3. Hypoalbuminemia (Serum albumin < 2.5 g %)
4. Hypercholesterolemia (Serum cholesterol > 200 mg %)  $\rightarrow \begin{cases} \uparrow \text{production of lipoprotein by the liver} \\ \uparrow \text{urinary excretion of lipase} \end{cases}$

## Incidence

2-3/100,000 children per year (But higher in underdeveloped countries)

## Etiology (Beyond 3 months of age)

### A) Idiopathic (1ry) NS (90%)

1. Minimal change NS (MCNS)\* [85%]
2. Mesangial proliferation
3. Focal segmental glomerulosclerosis (FSGS)
4. Membranous glomerulopathy
5. MPGN

### B) Secondary NS (10%)

#### 1. Glomerular diseases

- Membranous glomerulopathy
- SLE, HSP, vasculitis
- MPGN
- Post infectious GN (APSGN)

#### 2. Malignancy (Hodgkin lymphoma)

- Mechanism: Lymphokines secreted by the tumor  $\uparrow \uparrow$  glomerular capillary permeability
- NS may precede or follow the development of lymphoma
- NS may resolve as the tumor regress & recur with tumor recurrence

#### 3. Infection: Malaria, Schistosomiasis, HBV, HCV, HIV $\rightarrow$ more in underdeveloped countries.

#### 4. Drugs: Gold, mercury, captopril, penicillamine, phenytoin, procainamide & NSAIDs

#### 5. Metabolic: Fabry disease, GSD, glutaric aciduria, mitochondrial cytopathies

#### 6. Glomerular hyperfiltration: Oligomeganephronia, morbid obesity

#### 7. Syndromes: Charcot-Marie-Tooth, Laurant-Moon-Biedl, Cockayne

## Hereditary Nephrotic Syndrome

	Gene	Protein coded	Locus	Disease (Presentation)
1-	NPHS1	Nephrin	19	Finish-type congenital NS
2-	NPHS2	Podocin	1	FSGS (AR familial SRNS)
3-	WT1	WT1	11	Isolated DMS Denys-Drash syndrome Frasier syndrome (FSGS) $\rightarrow$ Wilms' Tumour
4-	LAMB2	Laminin $\beta$ 2	3	Pierson (Ocular; microcoria) $\rightarrow$ narrowing of the pupil
	LMX1B	Lmx1b	9	Nail-patella syndrome
	ACTN4	$\alpha$ -Actinin 4	19	FSGS (AD)
	TRPC6	TRPC6	11	FSGS (AD)
	CD2AP	CD2AP	6	FSGS (AD)

CD2AP: CD2 associated protein

TRPC6: Transient receptor potential cation channel 6

# Idiopathic Nephrotic Syndrome ✱

## (MCNS)

*Minimal Change NS*

### ✱ Definition ➡

4

### ✱ Incidence

- It is the commonest cause of NS in children (90%)
- Age: 2-6 yrs
- Sex: (♂:♀ = 2:1)

### ✱ Pathology :-

- ☒ L/M: No change or mild mesangial proliferation
- ☒ E/M: Fusion (effacement) of the foot processes of podocytes

### ✱ Pathology of Idiopathic NS ✱

	MCNS	Mesangial proliferation	FSGS
L/M	Normal	Mesangial proliferation (↑↑ cells + ↑↑ matrix)	Mesangial proliferation + Segmental scarring
I/F	Negative	Mesangial IgM ± IgA	IgM & C <sub>3</sub>
E/M	Fusion (effacement) of podocyte foot processes		
Frequency	85%	5%	10% (increasing)
Response to steroid	95%	50%	20% (ESRD in most cases)

### ✱ Pathophysiology :-

#### A) Heavy range proteinuria

Due to ↑↑ glomerular capillary permeability

? T call dysfunction → loss of negative charges → proteinuria

#### B) Hypoproteinemia

↓↓ Oncotic pressure → edema

#### C) Generalized edema due to:

• Hypoalbuminemia

• Salt & water retention [↓↓ Effective plasma volume → ↑↑ Aldosterone + ↑↑ ADH]

• Primary renal avidity to Na & water reabsorption

#### ✱ D) Hyperlipidemia

• ↑↑ Hepatic lipoprotein synthesis

• ↓↓ Lipoprotein lipase → urinary excretion

Oncotic pressure =  
Osmotic pressure of plasma proteins

## Clinical Picture

### 1. Generalized edema:

- Site of **onset**: Periorbital (more apparent in morning & ↓↓ at the end of the day)
- **March**: Then becomes generalized;

- LL edema
- Ascites
- Pleural effusion
- Scrotal / Labial edema

- **Character**: Pitting

2. Anorexia, nausea, vomiting, abdominal pain
3. Pallor: Edema & anemia (*Dilutional*)
4. Oliguria & frothy urine (Proteinuria)
5. BP: normal but may be elevated (↑↑ rennin-angiotensin system)
6. RR: ↑↑ with chest infection, pleural effusion, ascites
7. No hypertension, No gross hematuria
8. NS has a relapsing nature: Remission & exacerbation

### Remember $\Delta O$

#### Abdominal pain in NS:

1. Intestinal wall edema
2. Mesenteric hypoperfusion
3. Peritonitis
4. Pancreatitis (due to hyperlipidemia)
5. Peptic ulcer (Gastritis)
6. Pyelonephritis

is due to  
↓ Bl.v

### Remember $\Delta O$

#### Respiratory Distress in NS:

1. Pneumonia
2. Pleural effusion
3. Marked ascites

## DD of Nephrotic syndrome:

### 1. Causes of generalized edema

	Mechanism	C/P
<b>Nephrotic</b>	Hypoalbuminemia (↓↓ OP)	Nephrotic syndrome (Describe)
<b>Nutritional</b>	Hypoalbuminemia (↓↓ OP)	Kwashiorkor (No Ascites)
<b>Hepatic</b>	Hypoalbuminemia (↓↓ OP)	Jaundice, hepatomegaly...
<b>Cardiac</b>	↑↑ Venous pressure	Tachycardia, Tachypnea, Tender hepatomegaly
<b>Allergic</b>	↑↑ Capillary permeability	History (exposure) + Itching + Urticaria (wheals)

aphn losing enteropathy.

### 2. MCNS Vs non-minimal NS

	MCNS	Non-MCNS
Age	2-6	Any age
Hematuria	Absent	Common
HTN	Normal BP	Hypertension
Renal function	Normal	May be impaired
Complement	• Normal	May be consumed
Selectivity (Proteinuria)	• Selective (alb)	Non-selective
Renal biopsy	Not indicated	Indicated (e.g., FSGS...)
Response to steroids	Good	Poor or (SRNS)

## \* Complications

### 1. Infection (The major complication)

#### Predisposing Factors:

- Edema, ascites "Culture medium"
- Urinary loss of Immunoglobulins
- ↓↓ Factor B (properdin system) *one of complement factor*
- ↓↓ Splenic perfusion (Functional hyposplenism) *esp in S/Sy has v. imp. role in immunity*
- Steroid & immunosuppressive therapy

#### Organisms:

- Bacterial infection: Pneumococci, Haemophilus influenza (capsulated)
- Viral infection: Varicella → Benign disease *except in immunocompromized pt*

#### Site of infection:

- Peritonitis
- Sepsis, Pneumonia, cellulitis, UTI

### 2. Thromboembolic events:

#### \* Predisposing Factors:

- Hemoconcentration
- Hyperlipidemia
- Urinary loss of natural anticoagulants (Antithrombin III, Protein C & S)
- ↑↑ Fibrinogen
- Thrombocytosis

#### \* Site: Arterial or venous

- Deep vein thrombosis, Pulmonary embolism
- Renal vein thrombosis, indwelling catheters

### 3. Hypovolemia: Precipitated by aggressive diuresis or diarrhea

### 4. ARF (Usually reversible) due to:

- Hypovolemia (Pre-renal failure)
- Bilateral renal vein thrombosis
- Interstitial nephritis (Drug-induced)

### 5. Other complications: Respiratory (RD) & cardiovascular (Hyperlipidemia)

### 6. Side effects of steroid therapy: → endocrine

- Hyperglycemia, 2ry DM
- ↑↑ appetite: Overweight & Obesity (Moon face & buffalo hump): Cushingoid facies
- Myopathy & muscle weakness
- Osteoporosis
- Skin (poor wound healing, striae)
- Delayed healing of wounds
- Infection
- Growth retardation
- Hypertension
- GIT: Gastric irritation & peptic ulcers
- Cataract
- Emotional lability, psychosis, memory disturbance

### 7. Side effects of other medications:-

- 10 Sp* a. Calcineurin inhibitors: Gingival hyperplasia, hirsutism, HTN, Nephropathy
- 10* b. MMF: GIT, leucopenia *Myco Folate Mefol*
- 10* c. Alkylating agents: Leukopenia, hemorrhagic cystitis, alopecia, malignancy, sterility  
(Dose-related oligospermia & premature ovarian failure)

## Investigations

### A) Laboratory

#### a. Urine

- Urinalysis: Proteinuria (3+ or 4+), casts (hyaline, granular & waxy)
- Urine Pr/Cr ratio > 2
- 24 hr urine proteins (> 40 mg/m<sup>2</sup>/ hr or simply > 50 mg/Kg/ day)
- Proteinuria is selective (Albumin & Low MW proteins)
- Microscopic hematuria (20%)

#### b. Blood

- Serum albumin < 2.5 g %
- Serum cholesterol > 200 mg %
- KFT & Complement (C<sub>3</sub> & C<sub>4</sub>): Normal
- CBC: Anemia, thrombocytosis, leukocytosis
- ↓↓ Na (Dilutional)
- ↓↓ K (due to ↑↑ Aldosterone) ↓ renal perfusion
- ↓↓ Total Ca [Corrected Ca = Actual Ca + 0.8 (4 - serum Albumin)]

### B) Imaging: Renal U/S

### C) Invasive: Renal biopsy (not routine), indicated in:

#### ① Pre-treatment (when MCNS is unlikely):

- ☒ Age at onset < 1 yr or > 10 yrs
- ☒ Gross hematuria
- ☒ Marked hypertension
- ☒ Family history of similar disease
- ☒ Renal impairment
- ☒ Hypocomplementemia (↓↓ C<sub>3</sub>)

② SRNS = Failure to achieve remission after 6 weeks of steroid therapy

## Monitoring Recommendations for children with NS

Disease Type	Clinical	Laboratory
SSRN	Weight, Growth, BMI, BP	UA
Frequent relapsing & SDNS	Weight, Growth, BMI, BP	Creatinine, lipids, UA
SRNS		
Therapy	Clinical	Laboratory
Steroids	Weight, Growth, BMI, BP	Glucose, lipids
Cyclophosphamide		Creatinine, CBC, UA
Mycophenolate mofetil		CBC, LFTs
Calcineurin inhibitors	BP	Creatinine, Electrolytes, Glucose, lipids, drug level
ACE-I/ ARB	BP	Creatinine, Electrolytes, CBC
HMG-CoA reductase inhibitors		Lipids, LFTs, CPK

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A



## Treatment:

### 1. Place of management

### 2. Diet:

- Salt restriction (1-2 g/day) *Recommended Daily Allowment*
- Protein intake: kept within RDA or mildly ↑↑ (by 1/3) *↑ ptn → injury to Filtration Barrier.*
- Fluid restriction in cases of hyponatremia
- Steroid ↑↑ appetite, so caloric intake should be controlled to avoid obesity

### 3. Diuretics: Cautiously (Risk of hypovolemia, ARF, ↓↓ K & thrombosis) in cases of edema

- Furosemide (1-2 mg/Kg/day)
- Spironolactone (2-4 mg/Kg/day)
- Hydrochlorothiazide (2-4 mg/Kg/day)

### 4. Salt-free albumin:

- Given in case of severe edema with intravascular volume depletion (Hemoconcentration)
- Dose of 0.5-1 g/ Kg every 12-24 hrs
- It should be given slowly (over 4 hrs) followed by furosemide

### 5. Antibiotics:-

- Prophylaxis against pneumococcal infection:
  - Oral penicillin
  - Pneumococcal vaccine (7vPCV) is recommended
- Prophylaxis against Varicella infection:
  - VZIG (within 72 hours)
- Therapeutic:
  - Peritonitis
  - Varicella: Acyclovir

### 6. Antiproteinuric agents: ACEIs alone or in combination with ARBs

### 7. Scrotal edema: Elevation by pillows (to ↑↑ fluid removal by the gravity)

### 8. Hyperlipidemia: HMG-CoA reductase inhibitors (no controlled studies) Statins

### 9. Steroid therapy

Infection should be excluded before start of steroid therapy:

- Flaring of infection
- ↓↓ Response to steroids

### Induction & maintenance of remission:

Prednisone (2 mg/Kg/day) divided into 3 doses after meals for complete 4 weeks:

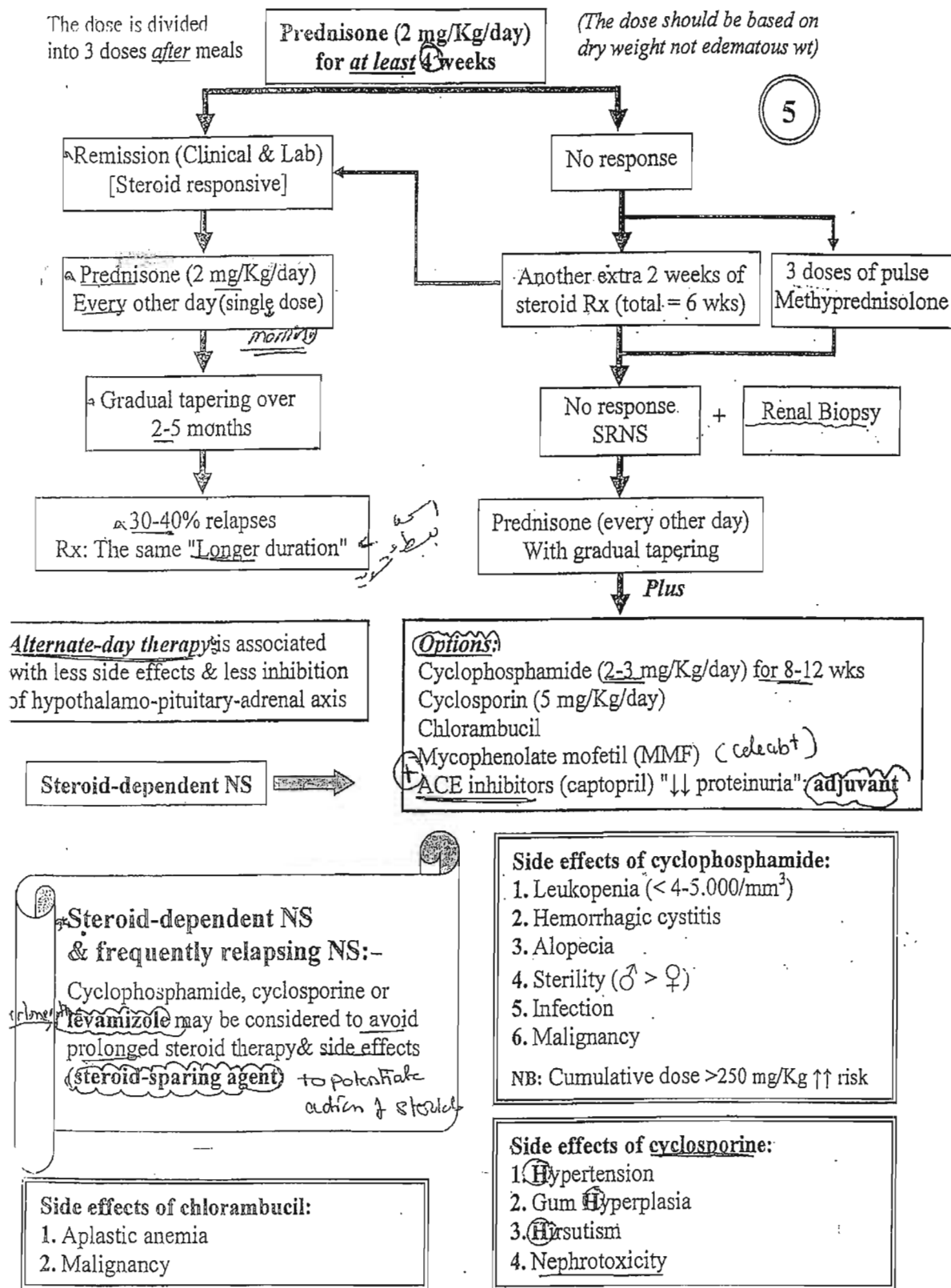
Infection should be excluded before start of steroid therapy:

#### ➤ Steroid responsive:

- Shift to alternate-day therapy (2 mg/Kg/day Single morning dose)
- Gradual tapering over 3-5 months

#### ➤ Steroid resistant (SRNS):

- Do renal biopsy
- Shift to alternate-day therapy...
- Pulse therapy with methylprednisolone may be given
- Add other immunosuppressive drugs
  - Cyclophosphamide (2-3 mg/Kg/day) for 2-3 months  
Monitoring of total leucocytic count is essential  
Stop cyclophosphamide if  $WBC < 4.000/mm^3$
  - Cyclosporin (5 mg/Kg/day)
  - Mycophenolate mofetil (MMF)
  - Others: Tacrolimus, Azathioprine, Vincristine, Chlorambucil



### Prognosis -

- Most children with idiopathic NS respond to Rx (50% of them have relapses)
- Relapses decrease as the child grows older
- Steroid responsive patients have good prognosis (regarding long-term renal function)
- SRNS (mostly FSGS) have much poorer prognosis (Ultimately ESRD)

# Nephrotic Syndrome during the 1<sup>st</sup> year

## Definition

Congenital NS: onset during the first 3 months of life

Infantile NS: onset during the first year (4-12 months)

## Etiology

### A. Secondary

1. **Infections:** CMV, Rubella, Syphilis, Toxoplasma, HBV, HIV
2. **SLE**
3. **Syndromes**
  - Denys-Drash syndrome [Ambiguous genitalia, Glomerulopathy (diffuse mesangial sclerosis), Wilms (usually bilateral)]. **R<sub>x</sub>:** bilateral nephrectomy
  - Nail-patella syndrome
  - Pierson syndrome
  - Cockayne syndrome

### B. Primary

1. **Congenital NS**
2. **Diffuse mesangial sclerosis**
3. **MCNS**
4. **FSGS**
5. **Membranous glomerulopathy**

## Congenital Nephrotic Syndrome

Scandinavian countries
---------------------------

## Etiology

The majority are due to mutation of one of 4 genes

Gene	Protein coded	Locus	Disease (Presentation)
NPHS1	Nephrin	19	Finish-type congenital NS (Scandinavian)
NPHS2	Podocin	1	FSGS (AR familial SRNS)
WT1	WT1	11	Isolated DMS Denys-Drash syndrome Frasier syndrome (FSGS)
LAMB2	Laminin $\beta$ 2	3	Pierson (Ocular, microcoria)

## Pathology

- Dilatation of PCT
- Mesangial hypercellularity
- Glomerular sclerosis

## Clinical picture (Onset = in the neonatal period)

- Prematurity
- Non-immune hydrops (edema)
- Placenta is large (> 25 % of birth weight)
- Generalized edema, ascites, umbilical hernia
- Cardiac RS

## Investigations (as idiopathic NS with the following differences)

- Non-selective proteinuria
- Loss of TBG → ↓↓ Thyroxine & ↑↑ TSH
- Renal biopsy (see pathology)
- Amniotic fluid  $\alpha$ -fetoprotein is ↑↑
- Genetic analysis

## Treatment

- Rx of the **secondary** causes
- Nutritional support & albumin infusion
- ACE inhibitors (↓↓ GFR & ↓↓ proteinuria)
- Indomethacin & Ibuprofen
- Unilateral nephrectomy
- Bilateral nephrectomy + Dialysis then renal transplantation
- Thyroid hormone replacement (may be started routinely)

**Steroids & immunosuppressives  
are of No value**

## Prognosis (Poor)

Death during the 1<sup>st</sup> 5 years of life due to:

- ▣ Infection
- ▣ Renal failure

# Acute Renal Failure

## (Acute Kidney Injury)

### Definition

- It is sudden (*Hours-Weeks*) reduction of renal functions to the point where body fluid, electrolyte & acid-base **homeostasis** can not be maintained
- It is usually associated with oliguria or anuria (NB: Non-oliguric ARF may occur with aminoglycoside toxicity)
- **Oliguria:** Urine volume  $< 400 \text{ cc/m}^2/\text{day}$  or  $< 1 \text{ cc/Kg/hour}$
- **Anuria:** Urine volume  $< 30 \text{ cc/m}^2/\text{day}$  or  $< 0.2 \text{ cc/Kg/hour}$
- The term **acute kidney injury** is preferred
- It is potentially **reversible**

### Incidence

- Pediatric tertiary care centers: 2-3%
- NICU: 8%

### Classification (=Stages of ARF)

#### A. Pediatric modified RIFLE (=PRIFLE)

Criteria	Estimated Creatinine Clearance	Urine Output
<b>Risk</b>	eCCI $\downarrow\downarrow$ by 25%	$< 0.5 \text{ cc/Kg/hour}$ for 8 hours
<b>Injury</b>	eCCI $\downarrow\downarrow$ by 50%	$< 0.5 \text{ cc/Kg/hour}$ for 16 hour
<b>Failure</b>	eCCI $\downarrow\downarrow$ by 75%	$< 0.3 \text{ cc/Kg/hour}$ for 24 hours
<b>Loss</b>	Persistent failure $> 4 \text{ wks}$	
<b>End-stage</b>	Persistent failure $> 3 \text{ months}$	

#### B. Acute Kidney Injury Network (AKIN Classification)

Stages	Rise of Serum Creatinine
<b>Stage I</b>	$\uparrow\uparrow > 150\%$
<b>Stage II</b>	$\uparrow\uparrow > 200\%$
<b>Stage III</b>	$\uparrow\uparrow > 300\%$

### Pathophysiology


- Oliguria/anuria
- Fluid, electrolyte & acid-base disturbance
  - Volume overload
  - $\uparrow\uparrow \text{ K} \ \& \ \uparrow\uparrow \text{ PO}_4$  (due to  $\downarrow\downarrow \text{ GFR}$ )
  - $\downarrow\downarrow \text{ Na}$  (Dilutional)
  - $\downarrow\downarrow \text{ Ca}$  (due to  $\uparrow\uparrow \text{ PO}_4$ )
  - Metabolic acidosis
- Retention of waste products (Uremic toxins)  $\rightarrow$  Hyperosmolarity

#### Effects of hyperosmolality:

1. Brain edema
2. Pulmonary edema
3. Renal failure
4. Cellular disruption

$$\begin{aligned} \text{Osmolality} &= 2\text{Na}^+ + \text{Glucose}/18 + \text{BUN}/3 \\ &= 285\text{-}295 \text{ mOsm/Kg} \end{aligned}$$

## Etiology & Pathogenesis of ARF

 <b>Prerenal</b> (Renal hypoperfusion)	<b>Intrinsic Renal</b>	<b>Postrenal</b> (Obstructive Uropathy)
<b>Etiology</b> 1. <b>Hypovolemia</b> ▫ Dehydration ▫ GIT losses (diarrhea) ▫ Hemorrhage ▫ Burns ▫ ↓↓ Effective plasma volume (NS) 2. <b>Hypotension</b> ▫ Shock (all types) ▫ DIC 3. <b>Hypoxemia</b> (Causes of respiratory failure)	1. <b>Acute Glomerulonephritis</b> ▫ RPGN (all causes) ▫ Postinfectious GN (APSGN) ▫ SLE, HSP, MPGN ▫ IgA nephropathy 2. <b>Vascular</b> ▫ MAHA: HUS, Renal vein thrombosis... ▫ Vasculitis 3. <b>Acute Interstitial Nephritis</b> ▫ Drugs (penicillin, cephalosporin, NSAID) ▫ Infection (sepsis, CMV, EB, HIV...) ▫ Disease associated: SLE, PUV... ▫ Idiopathic 4. <b>Acute Tubular Necrosis (ATN)</b> ▫ Uncorrected prerenal or postrenal ARF ▫ Drugs: aminoglycosides, amphotericin B... ▫ Heavy metals & IV contrast 5. <b>Tumors</b> ▫ Infiltration ▫ Tumor lysis syndrome (↑↑ Uric acid & PO <sub>4</sub> ) ▫ Treatment, How? 6. <b>Pigment nephropathy:</b> ▫ Myoglobinuria: Crush injury, Convulsions ▫ Hemoglobinuria: Acute hemolysis	1. <b>Kidney</b> ▫ Pelviureteric junction obstruction (PUJ) 2. <b>Ureters</b> ▫ Ureterovesical junction obstruction ▫ Bilateral 1ry megaureter 3. <b>UB/Urethra</b> ▫ Posterior urethral valve (PUV) ▫ Neurogenic bladder ▫ Hemorrhagic cystitis ▫ Stricture ▫ FB 4. <b>At any site:</b> Tumors, Trauma, Stones
<b>Pathogenesis</b> ↓↓ Renal blood flow → ↓↓ GFR Can be reversed (Rx of the cause) Uncorrected cases progress to intrinsic RF	Tubular damage (obstruction & back-leak) Vascular effects (↓↓ RBF & ↓↓ GFR)	↑↑ Bowman's capsule hydrostatic P → ↓↓ GFR Can be reversed (Rx of the cause) Uncorrected cases progress to intrinsic RF

## Clinical picture

- History of:
  - Preceding GE. *Causes of ARF following GE*
  - Preceding sore throat (APSGN)
  - Rash & arthralgia (SLE & HSP)
  - Antenatal hydronephrosis, interrupted urine stream, palpable UB, UTL (PUV)
  - Infection-associated ARF (APSGN, HUS, sepsis, antibiotic-related)
- Signs of circulatory overload (*mention?*)
- Signs of hypovolemia (dehydration) in prerenal ARF
- Oliguria/ anuria
- Acidotic breathing (Kussmaul's breathing = Rapid deep)
- Flank masses [PKD, renal vein thrombosis, hydronephrosis & tumors]

## Investigations

### A) Laboratory

- Urinalysis (may show proteinuria, hematuria, pyuria, eosinophiluria)
- CBC: Dilutional anemia (fragmented RBCs in HUS,  $\downarrow\downarrow$  WBC in SLE,  $\downarrow\downarrow$  PLT in SLE, HUS)
- KFT:  $\uparrow\uparrow$  (Creatinine & BUN)
- Electrolytes: Na, K, Ca,  $\text{PO}_4$  (??)
- Blood gases: Metabolic acidosis
- Investigation of the cause (ASOT, ANA, Anti-DNA Ab,  $\text{C}_3$ ,  $\text{C}_4$ , ESR...)

ARF diagnosis	Urinalysis
Prerenal ARF	Normal
GN	RBC, red cell casts, proteinuria
ATN	Granular casts, epithelial cells
Interstitial nephritis	RBC, WBC, granular casts, eosinophils
Vascular	Normal or RBC, proteinuria
Postrenal ARF	Normal or RBC, WBC, casts

### ECG changes in $\uparrow\uparrow$ K

1.  $\uparrow\uparrow$  PR interval
2. Wide QRS
3. Tall peaked T wave\*
4. VF
5. Cardiac arrest

### B) Imaging:

- Renal U/S: Swollen, echogenic, preserved C/M back pressure changes in postrenal ARF
- CXR (Cardiomegaly, pulmonary congestion  $\pm$  APE)
- ECG ( $\uparrow\uparrow$  K)

### C) Invasive: Renal biopsy may be indicated in unexplained intrinsic ARF

## Novel markers of ARF

- Serum creatinine is a relatively inaccurate & delayed marker of renal impairment
- Other markers: Cystatin C, NGAL, Urinary IL-18, KIM-1

Marker	Significance
Serum Cystatin C	Earlier & better correlation with GFR than serum creatinine
Plasma NGAL	↑↑ Serum level precedes ↑↑ serum creatinine by 2 days
Urinary NGAL	↑↑ Urinary level precedes ↑↑ serum creatinine by 2 days
Urinary IL-18	↑↑ Urinary level after ischemia
Kidney Injury Molecule-1 (KIM-1)	↑↑ Urinary level after ischemia

NGAL: Neutrophil Gelatinase-Associated Lipocalin

## Indices of ARF: (DD of Prerenal & Intrinsic ARF)

	Prerenal ARF	Intrinsic ARF
Urine Na	< 20 mEq/L	> 40 mEq/L
FENa	< 1%	> 2%
Specific gravity	> 1020	< 1010
Urine osmolality	> 500 mOsm/Kg	< 350 mOsm/Kg
Urea/Creatinine	> 20 (↑↑ urea reabsorption)	< 20

Fractional excretion of Na  
=  $\frac{\text{Urine Na} / \text{Plasma Na}}{\text{Urine Cr} / \text{Plasma Cr}}$

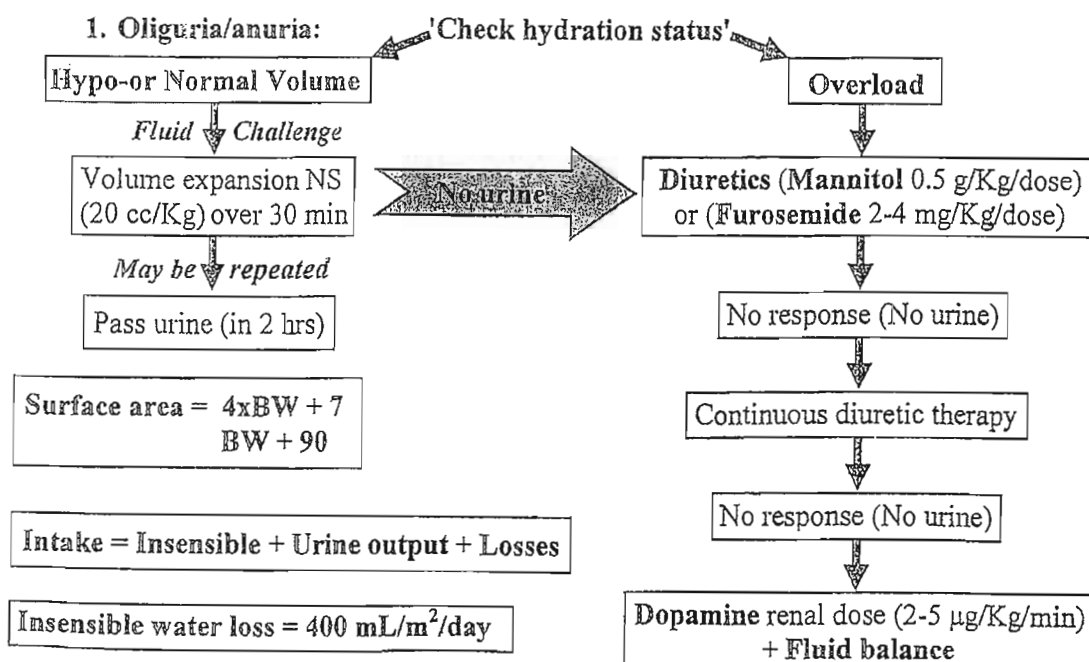
## Treatment

**Clinical monitoring:** Vital signs, level of consciousness, wt, urine output, losses, hydration

**Laboratory monitoring:** Electrolytes, blood gases, KFTs, ECG, ± CVP

**Post renal ARF:** Urologic consultation for relief of obstruction (catheter in PUV)

### A) Conservative





2. **Metabolic acidosis:**  $\text{HCO}_3^-$  "mEq" needed =  $1/3 \text{BW} \times \text{Deficit}$  (over 15-30 min)  
 Rapid correction of acidosis  $\rightarrow$  Tetany. Why?

3. **Hyperkalemia** ( $\text{K} > 6 \text{ mEq/L}$ ): (See before APSGN)

4. **Hyponatremia:**

- Fluid restriction-
- Hypertonic saline 3%: in symptomatic hyponatremia (lethargy & seizures) & if  $\text{Na} < 120 \text{ mEq/L}$
- mEq NaCl required =  $0.6 \times \text{BW} \times (125 - \text{serum Na})$

5. **Hypocalcemia & hyperphosphatemia**

- $\downarrow\downarrow \text{PO}_4$  intake
- $\text{PO}_4$  Binders e.g., Sevelamer (*Renagel*), Ca carbonate, Ca acetate. Aluminum-containing binders "Mucogel" *should be avoided* Toxicity: bone & CNS
- Ca gluconate IV is indicated in symptomatic hypocalcemia (tetany/seizures)

6. **Hypertension**

- Salt & water restriction and diuretics
- Ca channel blockers (Nifedipine 0.5-3 mg/Kg/day), Amlodipine, Isradipine
- Hydralazine IV (0.1-0.5 mg/Kg/dose)
- Propranolol (0.5-4 mg/Kg/day)
- Labetalol (4-40 mg/Kg/day)
- Na nitroprusside (0.5-10  $\mu\text{g/Kg/min}$ )
- ACE inhibitors are not recommended. Why?

7. **Convulsions**

- Rx of the cause (HTN,  $\downarrow\downarrow \text{Na}$  &  $\downarrow\downarrow \text{Ca}$ )
- Diazepam 0.3-0.5 mg/Kg/dose
- Dialysis

8. **Anemia:** Slow transfusion of packed fresh RBC if  $\text{Hb} < 7 \text{ g\%}$

9. **Infection**

- Avoid nephrotoxic drugs
- Renal adjustment of drugs (by  $\downarrow\downarrow$  the dose or  $\uparrow\uparrow$  the dose interval)

10. **Nutrition**

- Dietary restriction (Proteins, Na,  $\text{PO}_4$ , K)
- Adequate caloric intake (TPN can be used)
- $\text{H}_2$  blockers as ranitidine is used to prevent GIT bleeding

**Potential risks of blood transfusion in ARF:**

1. HTN
2. HTN
3. APE
4. Hyperkalemia

**B) Renal replacement therapy:** (= Failure of conservative measures)

**Indications of dialysis in ARF**

Clinical	Laboratory
▪ Anuria with volume overload	▪ Blood urea $> 100-150 \text{ mg/dL}$
▪ Acidosis	▪ Rapidly rising KFTs
▪ APE	▪ Intractable metabolic acidosis
▪ Bleeding (platelet dysfunction)	▪ Hyperkalemia not responding to..
▪ Pleurisy & pericarditis (Rub)	▪ Hyponatremia with volume overload
▪ Convulsions, confusion & coma	▪ Hyperphosphatemia & hypocalcemia

**Note:** Dialysis may be indicated to provide adequate nutritional intake

## Modalities of dialysis in ARF

1. **Acute peritoneal dialysis:** "Most common modality in infants & small children"
  - Peritoneal catheter is inserted per-cutaneously or surgically
  - Hyperosmolar fluid "dialysate" is infused into the peritoneal cavity
  - Usual dialysate: Glucose 1.7% or 4.25%
  - Dialysate is allowed to stay for a period 15-60 min "Dwell time", then be drained
  - The semipermeable peritoneal membrane is used for equilibrium between dialysate & body fluid
  - This cycle is repeated for 24-48 hours
  - Major complications: peritonitis, hernia, protein loss, respiratory compromise, hyperglycemia
2. **Acute hemodialysis:** "Extracorporeal therapy"
  - HD is more efficient than PD
  - Session is 2-4 hours
  - Rapid correction of volume overload, hyperkalemia & metabolic acidosis
  - Vascular access is needed (central venous catheters)
  - Complications:
    - ☒ Complications of VA:
      - Insertion: arterial injury, pneumothorax & hemothorax
      - Infection (local & systemic)
      - Thrombosis
    - ☒ Complications of the procedure:
      - Hypotension
      - Dysequilibrium (Rapid reduction of urea level). Mannitol can be used. Why?
      - Heparin (bleeding)
3. **Continuous renal replacement therapy (CRRT):** "Extracorporeal therapy"
  - Useful in hemodynamically unstable patients
  - Slow correction over 24 hours or more
  - Vascular access is needed (central venous catheters)
  - Modalities:
    - ☒ Continuous HD
    - ☒ Continuous hemofiltration
    - ☒ Continuous hemodiafiltration
    - ☒ Slow continuous ultrafiltration

## Prognosis

- Prognosis depends on the 1<sup>st</sup> etiology (rather than on the ARF itself)
- Good in APSGN & properly managed pre- & postrenal causes
- Recovery is unusual in RPGN, bilateral renal vein thrombosis & cortical necrosis

## Tubular Disorders

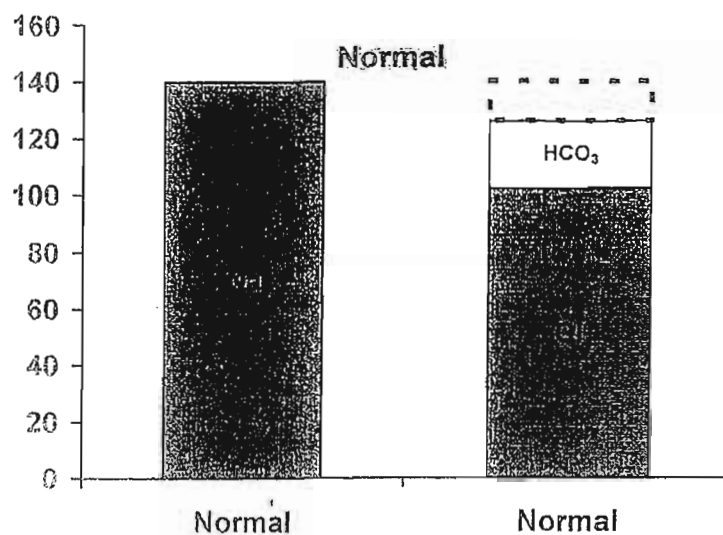
### Tubular Function

	PCT	Loop of Henle	DCT	Collecting ducts
Na	Reabsorption (60-70%)	Reabsorption 25% (thick) NaK2Cl transporter	Reabsorption 10-20% (Aldosterone)	
K	Reabsorption 60-70%	Reabsorption 25% (thick) NaK2Cl transporter	Secretion (Urine flow rate, Na delivery, Blood pH, Aldosterone)	
H <sub>2</sub> O	Reabsorption 60-70%	Reabsorption 25% (thin)	-	Reabsorption variable (ADH)
HCO <sub>3</sub>	Reabsorption 85%		Reabsorption 15%	
Ca	Reabsorption 60-70%	Reabsorption 20% (thick)	Reabsorption 10% (PTH)	
PO <sub>4</sub>	Reabsorption 60-70% (# by PTH)	Reabsorption 30%		
Mg	Reabsorption 30%	Reabsorption* 65%	Reabsorption 5%	
Glucose aa	Reabsorption (100%) with Na			
Urine Acidification	-	-	H <sup>+</sup> secretion NH <sub>4</sub> production	
Diuretics	CA inhibitors (acetazolamide)& Osmotic diuretics (Mannitol)	Loop (furosemide) # NaK2Cl	Thiazides # NaCl cotransporter	Amiloride & Triamterene (# ENaC) Spironolactone (#aldosterone R)

### Diuretics

	Example	Site of action	Action	Side effects	Uses
CA Inhibitors	Acetazolamide		# Carbonic anhydrase	↓↓ K	Pseudotumor cerebri
Loop (Most potent)	Furosemide	Loop of Henle	# NaK2Cl transporter	↓↓ K, alkalosis Hypercalcuria	Used with markedly ↓↓ KFT
Thiazides	Hydrochloro- thiazide	PCT	# NaCl co-transporter	↓↓ K, alkalosis Hypercalcemia	Effective only with normal KFT
K sparing	Amiloride & Triamterene	Collecting ducts	(# ENaC)	↑↑ K Gynecomastia	
	Spironolactone	Collecting ducts	(# Aldosterone R)		
Osmotic	Mannitol	PCT	Osmotic retention of H <sub>2</sub> O	Pseudo- Hyponatremia	Brain edema, ARF

# Metabolic Acidosis



$$\text{Cations} = \text{Anions} \quad [140 = 100 + 28]$$

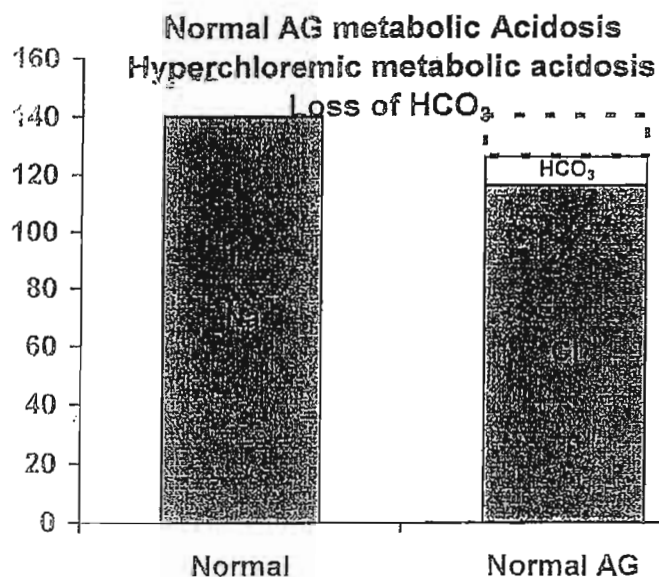
Cations = Na, K, Ca, Mg

Anions:

- ▣ Measurable = Cl, HCO<sub>3</sub>, PO<sub>4</sub>
- ▣ Unmeasurable = Acids

$$\text{Anion Gap} = \text{Na} - (\text{Cl} + \text{HCO}_3)$$

Normal AG = 8-16 mEq/L



**Metabolic Acidosis**

pH ↓↓ (7.35-7.45)

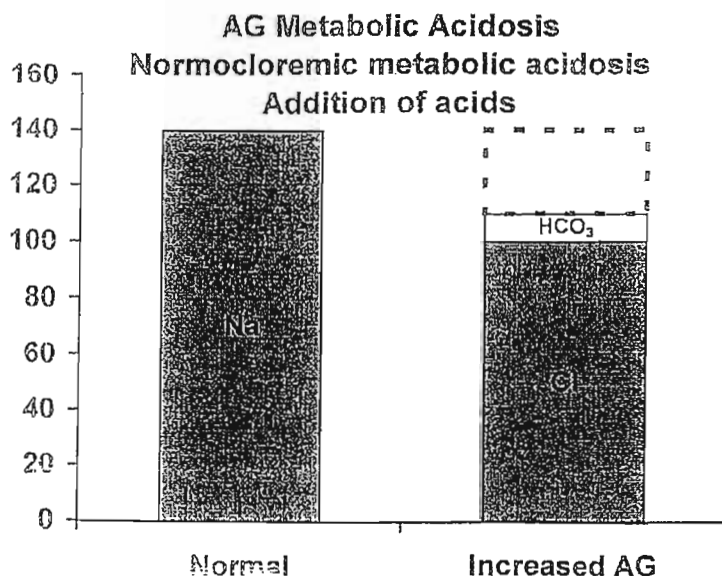
HCO<sub>3</sub> ↓↓ (20-28 mEq/L)

CO<sub>2</sub> ↓↓ (35-45 mmHg)

CO<sub>2</sub> = 3/2 (HCO<sub>3</sub>) + 8 ± 2

Loss of HCO<sub>3</sub> occurs via

1. GIT Diarrhea
2. Kidney: RTA



**Addition of acids:**

1. Exogenous: salicylates
2. Endogenous:
  - ▣ Lactic acidosis
  - ▣ DKA
  - ▣ Metabolic diseases

# Renal Tubular Acidosis

## Definition

It is a chronic state of persistent normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis) due to renal tubular defect:

- A) Failure of PCT  $\text{H}_2\text{CO}_3$  reabsorption [Proximal RTA=Type II]
- B) Failure of DCT  $\text{H}^+$  secretion [Distal RTA= Type I]
- C) Hyperkalemic RTA [Type IV]

Proximal RTA (Type II)	Distal RTA (Type I)	Hyperkalemic RTA (Type IV)
<b>Etiology</b> <b>1. Isolated (rare)</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Sporadic</li> <li><input checked="" type="checkbox"/> Hereditary</li> </ul> <b>2. Fanconi</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Primary</li> <li><input checked="" type="checkbox"/> Secondary                             <ul style="list-style-type: none"> <li>▪ Cystinosis</li> <li>▪ Galactosemia</li> <li>▪ Fructosemia (H. Fructose...)</li> <li>▪ Tyrosinemia</li> <li>▪ Wilson</li> <li>▪ Lowe syndrome</li> <li>▪ Fanconi-Bickel \$</li> <li>▪ Heavy metals</li> <li>▪ Cyclosporine</li> <li>▪ Gentamicin</li> <li>▪ Cisplatin, ifosfamide</li> </ul> </li> </ul>	<b>1. Primary</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Sporadic</li> <li><input checked="" type="checkbox"/> Hereditary</li> </ul> <b>2. Secondary</b> <ul style="list-style-type: none"> <li>▪ Interstitial nephritis</li> <li>▪ Obstructive. Uropathy</li> <li>▪ VUR</li> <li>▪ Pyelonephritis</li> <li>▪ Sickle cell anemia</li> <li>▪ SLE</li> <li>▪ Nephrocalcinosis</li> <li>▪ Medullary sponge kidney</li> <li>▪ Amphotericin B</li> <li>▪ Lithium</li> <li>▪ Cisplatin</li> </ul>	<b>1. Primary</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Sporadic</li> <li><input checked="" type="checkbox"/> Hereditary</li> </ul> <b>2. Secondary</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Hypoaldosteronism                             <ul style="list-style-type: none"> <li>▪ CAH</li> <li>▪ Addison</li> </ul> </li> <li><input checked="" type="checkbox"/> Pseudo-(End organ)</li> <li><input checked="" type="checkbox"/> Hyporeninemia 2<sup>ry</sup> <ul style="list-style-type: none"> <li>▪ Interstitial nephritis</li> <li>▪ Obst. uropathy</li> <li>▪ VUR</li> <li>▪ Pyelonephritis</li> <li>▪ Sickle cell anemia</li> <li>▪ SLE</li> <li>▪ Cyclosporine</li> </ul> </li> </ul>
<b>Pathophysiology</b> <del>↓ PCT <math>\text{HCO}_3^-</math> reabsorption</del> (defective Na/H exchanger) <b>Bicarbonaturia → Acidosis</b> $\uparrow\uparrow \text{NaHCO}_3$ delivery to DCT → $\uparrow\uparrow \text{Na}$ reabsorption & $\uparrow\uparrow \text{K}$ secretion ( $\downarrow\downarrow \text{K}$ ) $\text{NaHCO}_3$ loss → <u>polyuria</u> & polydipsia $\downarrow\downarrow \text{ECV} \rightarrow \uparrow\uparrow \text{Renin} \rightarrow 2^{\text{ry}}$ $\uparrow\uparrow \text{Aldosterone} \rightarrow \downarrow\downarrow \text{K}$ $\downarrow\downarrow \text{K} \rightarrow$ Muscle weakness, <u>polyuria</u> , constipation Acidosis → <b>Bone breakdown</b> ( $\text{CaCO}_3$ acts as a buffer) Hypercalciuria ( <i>Normal citrate</i> ) $\downarrow\downarrow \text{PO}_4 \rightarrow$ in Fanconi (Rickets) Normal urine acidification Urine pH < 5.5 (during acidosis)	<del>↓ DCT <math>\text{H}^+</math> secretion</del> $\downarrow\downarrow \text{HCO}_3^-$ reabsorption $\downarrow\downarrow$ Acid secretion <b>Bicarbonaturia → Acidosis</b> $\text{NaHCO}_3$ loss → <u>polyuria</u> & polydipsia $\downarrow\downarrow \text{ECV} \rightarrow \uparrow\uparrow \text{Renin} \rightarrow 2^{\text{ry}}$ $\uparrow\uparrow \text{Aldosterone} \rightarrow \downarrow\downarrow \text{K}$ $\downarrow\downarrow \text{K} \rightarrow$ Muscle weakness, polyuria, constipation Acidosis → <b>Bone breakdown</b> Hypercalciuria ( $\downarrow\downarrow$ <i>Citrate</i> ) Renal stones & nephrocalcinosis Impaired urine acidification Urine pH > 5.5 (during acidosis)	<del>↓ Mineralocorticoids</del> $\downarrow\downarrow \text{H}^+$ secretion $\downarrow\downarrow \text{K}$ secretion $\downarrow$ <b>Acidosis</b> <b>Hyperkalemia</b> <b>Treatment</b> 1. Sodium polystyrene sulfonate orally (Na Kayexalate) 1 g/Kg 2. Rx of the cause

**Clinical picture** (Onset = in the first few months\*)

- Polyuria, polydipsia, FTT, vomiting (acidosis), constipation & hypotonia ( $\downarrow\downarrow$  K)
- Frequent attacks of dehydration & fever
- Respiratory distress (acidotic breathing. DD = pneumonia)
- Rickets, bony pains & pathological fractures specially in Fanconi syndrome ( $\downarrow\downarrow$   $\text{PO}_4$ )
- $\downarrow\downarrow$  Ca & tetany may develop during correction of acidosis (alkalosis  $\rightarrow \downarrow\downarrow \text{Ca}^{+2}$ )
- Picture of the cause

**Investigations**

- Blood gases: Normal AG metabolic acidosis (hyperchloremic metabolic acidosis)
- $\downarrow\downarrow$  K (more in type II) and  $\uparrow\uparrow$  K in type IV
- Renal function is usually preserved (except in cystinosis, dehydration "prerenal"...)
  - Urine AG  $[\text{Na} + \text{K} - \text{Cl}]$ : Positive in type I (Impaired  $\text{NH}_3$  &  $\text{NH}_4\text{Cl}$  secretion)
  - Negative in type II ( $\uparrow\uparrow$   $\text{NH}_3$  &  $\text{NH}_4\text{Cl}$  secretion)
- Urine pH (during acidosis): Type I  $> 5.5$   
Type II  $< 5.5$
- Daily requirements of  $\text{HCO}_3^-$ : Type I 2-4 mEq/Kg/day  
Type II 2-20 mEq/Kg/day
- Urinalysis: glycosuria, aminaciduria & phosphaturia ( $\text{PO}_4$  / Cr. ratio) in Fanconi syndrome
- Renal US: Nephrocalcinosis & renal stones in type I (hypercalcuria +  $\downarrow\downarrow$  citrate)

**Treatment:****A) Treatment during dehydration:****a. Correction of Dehydration**

Saline: D5% (1:1). The amount depends on the degree of dehydration

**b. Correction of Hypokalemia**

K concentration up to 40 mEq/L can be used

**c. Correction of Acidosis**

mEq  $\text{HCO}_3^-$  "base" needed =  $0.3 \times \text{BW} \times \text{Deficit}$  (Deficit = 15 - actual  $\text{HCO}_3^-$ )

Given over 15-30 minutes

▫  $\text{NaHCO}_3$  5% (1 cc = 0.6 mEq  $\text{HCO}_3^-$ )

▫  $\text{NaHCO}_3$  8.4% (1 cc = 1 mEq  $\text{HCO}_3^-$ )

**B) Maintenance therapy for hydration, acidosis & hypokalemia****a. Adequate fluid intake**

Free access to water

**b. Potassium therapy (Oral)**

The dose is adjusted according to K level (K syrup 1cc = 0.4 mEq).

**c. Correction of Acidosis (Oral)**

Start with 2 mEq / Kg / day, and then gradually increase the dose ()

▫  $\text{NaHCO}_3$  5% or 8.4%

▫ Polycitra (1 cc contains 1 mEq K + 1 mEq Na + 2 mEq  $\text{HCO}_3^-$ ): is better used

**C) Phosphate supplementation for Fanconi syndrome****D) Thiazides for hypercalciuria****E) Treatment of the cause (Cysteamine for cystinosis)****Prognosis**

Early diagnosis & Rx improve prognosis

Renal failure in cystinosis & nephrocalcinosis

**DD**

1. Metabolic acidosis

2. DD of RTA

**DD of the cause RTA:**

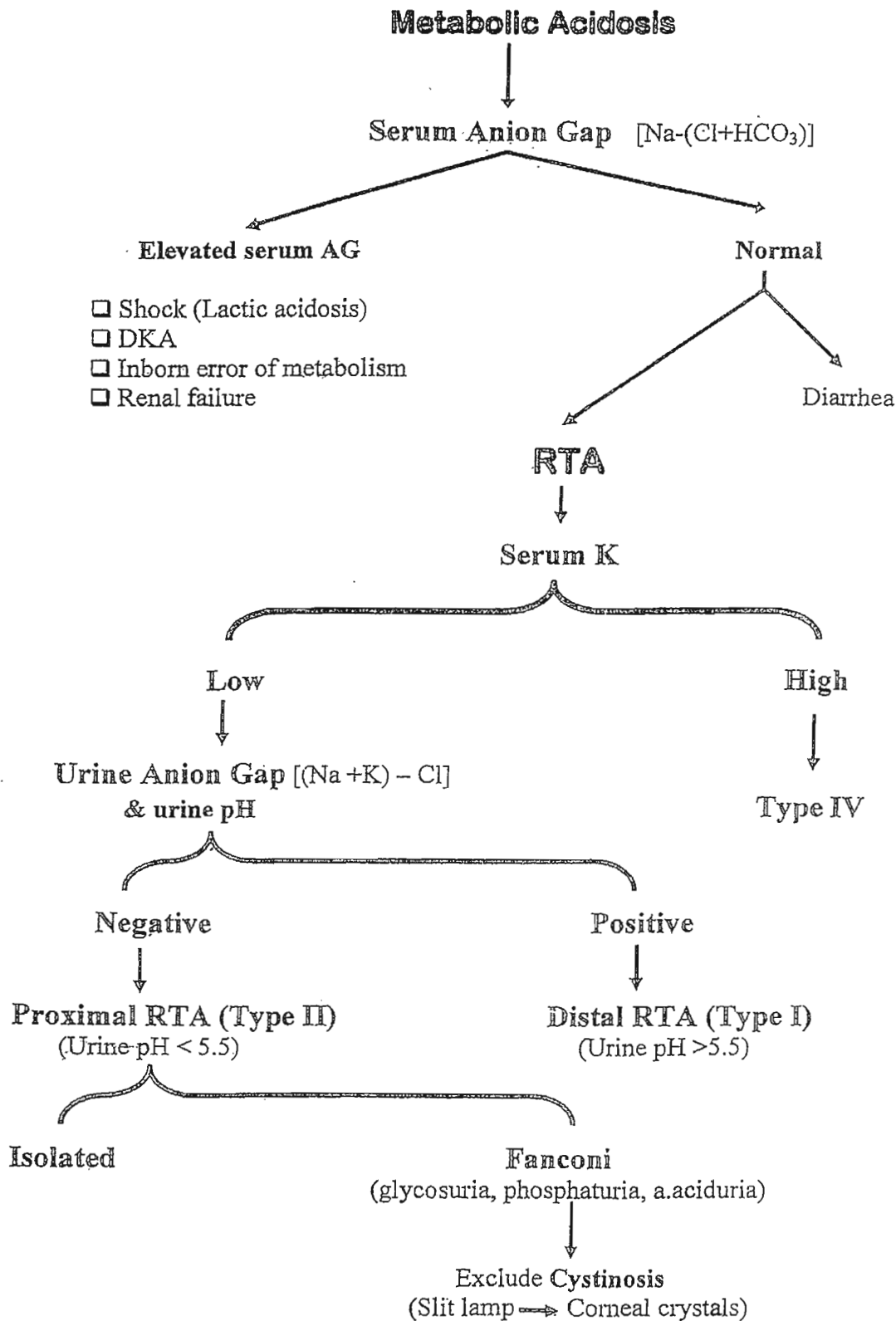
- $\downarrow\downarrow$  K
- FTT
- Rickets
- Daily  $\text{HCO}_3^-$  requirement
- Nephrocalcinosis
- Renal stones
- Urine pH
- Urine AG
- Urine (G,  $\text{PO}_4$ , aa)
- Urine citrate

# Approach to Metabolic Acidosis& RTA

## Clinical Clues for Diagnosis:

FTT, RD, recurrent episodes of vomiting & dehydration and constipation.

**NB:** Nephrocalcinosis may be detected in patients with distal RTA.



# Cystinosis

## Definition

It is AR disease caused by a defect in cystine metabolism with accumulation of cystine crystals in the lysosomes of many organs (kidneys, liver, eye, brain, and thyroid)

## Incidence

1: 100.000

## Pathogenesis

Mutation of CTNS gene which encodes cystinosis protein (Lysosomal cystine transporter)

→ Accumulation of cystine in the lysosomes → Tissue damage

## Clinical picture

### A) Infantile (Nephropathic cystinosis)

Onset: 1<sup>st</sup> year

Course: ESRD by the end of the 1<sup>st</sup> decade (if not treated)

C/P:

Fanconi syndrome (Polyuria, polydipsia, FTT, vomiting, dehydration, acidosis, rickets)

Fair skin (blond)

Photophobia

Hypothyroidism

HSM

ESRD

### B) Adolescent form: Less severe & slowly progressive

### C) Adult form: No renal disease

## Diagnosis

1. Slit lamp examination: Corneal crystals

2. Leukocyte cystine conte

3. Prenatal genetic diagnosis

4. Investigation of RTA & CRF

The presence of **corneal crystals** is **diagnostic** of cystinosis, although crystals may be absent < 1 yr of age

## Treatment

1. Cysteamine (Oral capsules) →
2. Cysreamine eye drops
3. Management of Fanconi syndrome (see before)
4. Management of CRF (see later)

Cysteamine converts cystine to cysteine facilitating lysosomal transport

Cornea is avascular

# Lowe Syndrome

(Oculocerebrorenal syndrome)

## Definition

It is XLR disease caused by a defective transport of vesicles within Golgi apparatus

## Pathogenesis

Mutation of OCRL1 gene

## Clinical picture

A) Ocular: Congenital cataract

B) Cerebral: Infantile hypotonia (Floppy), mental retardation, stereotypy (repetitive behavior)

C) Renal: Fanconi syndrome

## Investigations OCR

Treatment Supportive + Rx of Fanconi syndrome



# Bartter Syndrome

## Definition

It is an AR syndrome characterized by hypokalemia, metabolic alkalosis & hypercalciuria

## Types

	(A) Neonatal Bartter syndrome	(B) Classic Bartter syndrome
<b>Onset</b>	Neonatal	Infancy or early childhood
<b>Severity</b>	More severe	Less severe
<b>Polyhydramnios</b>	Present	Often present
<b>Nephrocalcinosis</b>	Present	Absent

## Genetic defects

Mutation of one of 3 genes coding for:

1. Na-K-2Cl transporter\*
2. ROMK channels
3. Basolateral Cl channels

## Pathogenesis

- $\downarrow\downarrow$  Na, K & Cl reabsorption in the thick ascending limb of Henle  $\rightarrow \downarrow\downarrow$  ECV  $\rightarrow \uparrow\uparrow$  Renin  $\rightarrow$  2ry  $\uparrow\uparrow$  Aldosterone  $\rightarrow \downarrow\downarrow$  K &  $\downarrow\downarrow$  H  $\rightarrow$  Hypokalemia & Alkalosis
- $\downarrow\downarrow$  K  $\rightarrow \uparrow\uparrow$  PGs  $\rightarrow \uparrow\uparrow$  Renin-angiotensin-Aldosterone axis (Normal BP)

## Pathology

Hyperplasia of the Juxtaglomerular apparatus

## Clinical picture -

- Antenatal history of polyhydramnios
- Polyuria, polydipsia, FTT, vomiting, constipation & hypotonia ( $\downarrow\downarrow$  K)
- Frequent attacks of dehydration & fever
- Blood pressure = Normal
- Dysmorphic facies: Triangular face, protruding ears & large eyes

## Investigations

- Blood gases: metabolic alkalosis
- K, Cl:  $\downarrow\downarrow$
- Renin, aldosterone & PGE:  $\uparrow\uparrow$
- Renal function is usually preserved (except in dehydration "prerenal"...)
  - Urine Na, K, Cl, Ca  $\uparrow\uparrow$
- Hypercalciuria [urine Ca / Creatinine ratio > 0.2 - 0.8]
- Renal US: Nephrocalcinosis (hypercalciuria)

## Treatment

### A) Treatment during dehydration

#### a. Correction of Dehydration

Saline: D5% (1:1). The amount depends on the degree of dehydration

#### b. Correction of Hypokalemia

K concentration up to 40 mEq/L can be used

### B) Maintenance therapy for hydration & hypokalemia

#### a. Adequate fluid intake

Free access to water

#### b. Potassium therapy (Oral)

The dose is adjusted according to K level (K syrup 1cc = 0.4 mEq)

### C) Indomethacin

Dose: 2 mg/kg/day

Mechanism:  $\downarrow\downarrow$  PGs  $\rightarrow \downarrow\downarrow$  Renin-angiotensin-Aldosterone axis  $\rightarrow \downarrow\downarrow$  K loss

Side effects: GIT renal impairment

#### DD of Bartter syndrome:

1. Polyuria: DM, DI, RTA...
2. Metabolic Alkalosis: vomiting, furosemide use, Cl losing diarrhea...

# Gitelman syndrome

(Bartter syndrome variant)

## Definition

It is an AR syndrome characterized by hypokalemia, metabolic alkalosis & hypocalciuria  
Often called "Bartter syndrome variant"

	Bartter syndrome	Gitelman Syndrome
"Similar to:"	Furosemide-like	Thiazide-like
Onset	Neonatal, infancy or early childhood	Late childhood or adulthood
Severity	More severe	Less severe
Defect	Na-K-2Cl transporter* (loop)	NaCl cotransporter (DCT)
Urinary Ca*	↑↑	↓↓
Mg*	Usually normal (may be ↓↓)	↓↓
Urinary Mg	normal	↑↑
Treatment	K + Indomethacin	K + Mg supplementation

## Inherited Renal Tubular Abnormalities

1. RTA (all causes)
2. Bartter syndrome
3. Gitelman syndrome
4. Nephrogenic DI
5. Isolated renal glycosuria
6. Cystinuria
7. Dent syndrome (XL nephrolithiasis)
8. Familial hypomagnesemia
9. Familial XL hypophosphatemic rickets
- 10 Pseudohypoaldosteronism
11. Glucocorticoid-suppressible hyperaldosteronism
12. Syndrome of apparent mineralocorticoid excess (Pseudohyperaldosteronism)
13. Liddle syndrome

### Cystinuria:

**Defect:** ↓↓ Renal reabsorption of COAL  
(cystine, ornithine, arginine, lysine)

**C/P:** Renal stones

**Rx:** Penicillamine

### Liddle syndrome:

**Defect:** Activation mutation of Na  
epithelial channels

**C/P:** HTN, ↓↓ K, ↓↓ PRA

**Rx:** HTN & ↓↓ K

### Isolated renal glycosuria:

**Defect:** ↓↓ PCT reabsorption of glucose

**C/P:** Accidentally discovered

**Rx:** Reassurance

### Dent syndrome (XL nephrolithiasis):

**Defect:** Hypercalciuria, Fanconi

**C/P:** Renal stones

**Rx:** ↑↑ Fluid intake + Thiazides

# **Tubulointerstitial Nephritis**

## **Definition**

It is tubulointerstitial inflammation & damage with relative sparing of glomeruli & vessels.  
According to the nature of inflammation, it is classified into acute & chronic forms

## **Classification**

	<b>Acute TIN</b>	<b>Chronic TIN</b>
<b>Pathology</b>	Tubular: necrosis, edema Interstitial: Lymphocytic infiltration ↑↑ Eosinophils (drug-induced)	Tubular: Atrophy Interstitial: Fibrosis
<b>Pathogenesis</b>	Immune-mediated (T cell)	
<b>Etiology</b>	<b>Drugs</b> <b>a. Antibiotics</b> Penicillins, Erythromycin, Cephalosporins Sulfonamides, tetracycline <b>b. Anticonvulsants:</b> Phenytoin, Phenobarbital, Na Valproate <b>c. Others</b> NSAID, Aspirin, Cyclosporine, Diuretics <b>Infection</b> Pyelonephritis, EBV, CMV, HBV, HIV <b>Disease associated</b> SLE, Sarcoidosis Acute rejection <b>Idiopathic</b>	<b>Drugs</b> <b>a. Analgesics:</b> NSAIDs, aspirin <b>b. Cyclosporine</b> <b>c. Heavy metals</b> (Lead, Gold, Mercury) <b>d. Lithium</b> <b>Infection</b> Pyelonephritis, EBV, HBV, HIV <b>Disease associated</b> Obstructive uropathy* VUR & Pyelonephritis Sickle cell anemia Nephrocalcinosis SLE, Sarcoidosis PKD (ARPKD & ADPKD) NPH-MCKD Chronic rejection Fabry, Alport, Wilson, Crohn TIN with uveitis syndrome <b>Idiopathic</b>
<b>Clinical Picture</b>	▪ Fever, Rash & Arthralgia ▪ Nausea, vomiting & anorexia ▪ ARF (mild-severe) ▪ Urine output: 30-40% are non-oliguric ▪ Picture of the cause: drug intake, SLE...	▪ Asymptomatic & non-specific ▪ Salt-loss (No HTN) ▪ CRF ▪ Urine output: Polyuria (Enuresis) ▪ Picture of the cause: (JN-MCKD)
<b>Diagnosis</b>	▪ Lab: - UA (RBC, WBC, granular casts, Eosinophils) - CBC (Eosinophils), KFT, electrolytes ▪ Imaging: U/S (swollen, echogenic...) ▪ Invasive: Renal biopsy (questionable cases)	▪ Lab: - UA, urine C&S, - KFT, electrolytes, CBC (anemia-JN) ▪ Imaging: U/S (small...), VCUG ▪ Invasive: Renal biopsy (not conclusive)
<b>Treatment</b>	▪ Avoid the offending agent (Diagnostic) ▪ Supportive (ARF) ▪ Steroids can hasten recovery & improve long-term prognosis ( ▪ ± Immunosuppressives?	▪ Avoid the offending agent ▪ Supportive (CRF) ▪ Rx of obstructive uropathy ▪ Rx of infection
<b>Prognosis</b>	- Complete recovery - Prolonged RF: Guarded prognosis	Depends on the cause ESRD is inevitable in Juvenile NPH

## Nephronophthisis-

### Medullary cystic kidney disease complex

#### A. Nephronophthisis

- Nephronophthisis is AR with 3 types (juvenile, infantile & adolescent)
- Affected gene: NPHP
- JN causes 10-20% of pediatric ESRD
- Clinical picture (Chronic TIN):
  - Polyuria, polydipsia
  - 2ry enuresis
  - Growth failure
  - Anemia (Unexplained & out of proportion of the degree of renal impairment)
- U/S: Cysts at the C/M junction
- Progression to ESRD is the rule
- Extra-renal manifestations:
  - a. Senior-Løken syndrome (Retinitis pigmentosa)
  - ✓ b. Joubert syndrome (Hypotonia, cerebellar ataxia, MR, gaze abnormalities)
  - c. Cogan syndrome (Oculomotor apraxia)
  - d. Hepatic fibrosis

Molar tooth sign  
MRI brain

#### B. Medullary cystic kidney disease

- Medullary cystic kidney disease is (AD)
- Presentation in adulthood
- No extra renal manifestations

## × α Cortical Necrosis ~

#### Etiology

- A) Neonates: HIE (asphyxia), sepsis, shock, CHD, dehydration, renal vein thrombosis
- B) After neonatal period: Septic shock & severe HUS

Pathogenesis: Endothelial cell injury & ↓↓ renal cortical blood flow

Pathology: Infarction, thrombosis, necrosis

Clinical picture: ARF + Picture of the cause

Investigations: ARF + Picture of the cause

Treatment: Supportive + Rx of the cause

Prognosis: Bad (CRF)

# Toxic Nephropathy

★ vs  
s.d  
S

## Incidence

Drugs causes 20% of AKI in children & adolescents

## Factors affecting the development of drug toxicity

1. Age
2. Medical condition
3. Hydration status
4. Exposure dose
5. Concomitant use of other drugs
6. Genetics

## Mechanism of nephrotoxicity

1. Alteration of RBF "Vasoconstriction" (Cyclosporine)
2. Tubular cell damage (Aminoglycosides)
3. Tubular lumen obstruction (IV contrasts)
4. Immune-mediated

## Renal syndromes caused by nephrotoxins

*Iatrogenic renal injury*

Renal syndrome	Drugs
<b>Nephrotic syndrome</b>	Gold, mercury, ACE inhibitors, NSAIDS, penicillamine, interferone, phenytoin
<b>RTA</b>	Heavy metals, Cyclosporine, Gentamicin, Outdated tetracycline, Cisplatin, Ifosfamide, Amphotericin B, Lithium
<b>Interstitial Nephritis</b>	See before
<b>Nephrogenic DI</b>	Amphotericin B, Lithium, Demeclocyclin
<b>Renal Vasculitis</b>	Isoniazide (INH), Sulfonamides, Hydralazine
<b>Nephrocalcinosis</b>	Furosemide, Bumetanide, Vitamin D, Allopurinol, Topiramate
<b>Thrombotic microangiopathy</b>	Cyclosporine, OCPs, HUS
<b>Obstructive uropathy</b>	Sulfonamides, Methotrexate, Acyclovir
<b>ARF</b>	<div style="display: flex; flex-wrap: wrap;"> <div style="flex: 50%;"> <ol style="list-style-type: none"> <li>1. Aminoglycosides</li> <li>2. Vancomycin</li> <li>3. Lithium</li> <li>4. Amphotericin B → <i>Fungicide</i></li> <li>5. Acyclovir</li> <li>6. Cyclosporine</li> <li>7. Tacrolimus</li> </ol> </div> <div style="flex: 50%;"> <ol style="list-style-type: none"> <li>8. Cisplatin</li> <li>9. Ifosfamide</li> <li>10. NSAID</li> <li>11. ACE inhibitors</li> <li>12. IV contrast</li> <li>13. Heavy metals</li> <li>14. Biologic toxins (snake, spider...)</li> </ol> </div> </div>

## Prevention of nephrotoxicity

1. Avoid IV contrast exposure (IVP, CT with contrast). Use U/S, MRI & renal scan instead
2. Avoid nephrotoxic agent (if possible)
3. Use the lowest effective dose for the least duration
4. Avoid simultaneous use of several nephrotoxic agents
5. Avoid dehydration
6. Monitoring of serum level

Useful medications should NOT be withheld because of potential nephrotoxicity; but...

N-acetylcysteine offer renoprotection when contrast studies are critical

# Chronic Renal Failure

## Definitions

**Chronic Kidney Disease (CKD):** It is renal injury &/or  $GFR < 60 \text{ ml/min/1.73m}^2$  for  $> 3\text{m}$   
It is *progressive & usually irreversible* reduction of renal functions

**End-Stage Renal Disease (ESRD):** It is the stage of chronic renal disease at which survival can not be maintained without renal replacement therapy (dialysis or transplantation)

## Stages of Chronic Kidney Disease

Stage	Description	GFR ( $\text{ml/min/1.73m}^2$ )
1	Kidney damage with normal or $\uparrow\uparrow$ GFR	$\geq 90$
2	Kidney damage with mild $\downarrow\downarrow$ GFR	60- 89
3	Moderate $\downarrow\downarrow$ GFR	30- 59
4	Severe $\downarrow\downarrow$ GFR	15-29
5	Kidney failure	$< 15$ (or on dialysis)

## Etiology

### 1. Glomerular

- RPGN (all causes)
- IgA nephropathy, Alport syndrome
- MPGN, Membranous glomerulopathy
- SLE, HSP
- Amyloidosis
- Sickle cell nephropathy

### 2. Nephrotic Syndrome

- FSGS
- SLE, HSP, MPGN, Membranous glomerulopathy
- Congenital NS (Finnish type...)

### 3. Vascular

- MAHA: HUS, Renal vein thrombosis...
- Vasculitis

### 4. Pyelonephritis & reflux nephropathy

### 5. Chronic interstitial nephritis

### 6. Cystic renal diseases

- AR polycystic kidney disease (ARPKD)
- AD polycystic kidney disease (ADPKD)
- Juvenile nephronophthisis-Medullary cystic kidney disease (NPH-MCHD)

### 7. Obstructive uropathy

- Congenital: PUV, PUJ obstruction
- Acquired: Renal stones (Oxalosis)

### 8. Development anomalies

Agenesis, aplasia, hypoplasia, dysplasia →

### 9. Tumors (Wilms)

### 10. RTA (Only in certain conditions)

- Cystinosis
- Nephrocalcinosis (Type I RTA)

### Hereditary causes of GRF:

1. Congenital NS
2. Cystinosis
3. Cystic renal diseases
4. Nephronophthisis
5. Alport syndrome
6. Oxalosis

**Agenesis:** Complete absence of the kidney

**Aplasia:** Extreme form of dysplasia

**Hypoplasia:** Small kidney with  $\downarrow\downarrow$  No. of glomeruli

**Dysplasia:** Abnormal renal differentiation

## Pathophysiology & Clinical Picture of CRF

The symptoms & signs of CRF are few, vague & non-specific. Moreover it may be asymptomatic. ARF may develop on top of pre-existing CRF. **Indicators of chronic renal disease include:** antenatal oligo-/ polyhydramnios, abnormal antenatal U/S, single umbilical artery, hypospadias, syndromes (e.g., Bardet-Biedl), positive family history, FTT, delayed puberty, late-onset rickets, unexplained anemia or seizures (High index...)

	Manifestation	Mechanism	Clinical Picture
Azotemia	1. Retention of waste products (uremic toxins)	↓ GFR	Headache, anorexia, nausea & vomitin Earthy color, pigmentation & pruritis
Fluid, Electrolytes & acid-base	2. Na ▪ Na retention ▪ Na loss	▪ In glomerular diseases (↑↑ Renin) ▪ In tubulo-interstitial diseases (Diuresis)	▪ Hypervolemia (?? Mention) ▪ Hypotension
	3. Hyperkalemia	↓ GFR, Acidosis	Arrhythmias
	4. Acidosis	↓ HCO <sub>3</sub> reabsorption & ↓ Acid secretion	RD (Acidotic breathing)
	5. Hypocalcemia & hyperphosphatemia	▪ ↓ GFR → ↑↑ PO <sub>4</sub> → ↓ Ca ▪ Activation of vitamin D	Renal osteodystrophy
Blood	6. Urine concentration defect	Tubular damage	Polyuria & polydipsia
	7. Anemia	See before	Pallor
	8. Bleeding	Platelet dysfunction	Bleeding
Skeletal	9. Infection	↓ Phagocytic function, instruments, VA	Fever
	10. Renal osteodystrophy (ROD)	↓ Vit.D, ↑↑ PTH, Acidosis, ↓ Ca absorption	Renal rickets, Fractures, Deformities, stature
	11. Growth retardation GH → resistance	Nutritional deficiencies, Acidosis, Anemia, Uremic toxins, ROD GH	FTT & Short stature
Systemic	12. Hypertension	Na retention, hypervolemia & ↑↑ Renin	HTN, HTN encephalopathy, cardiom
	13. Cardiomyopathy	Uremic toxins, HTN	HF
	14. Pericarditis	Uremic toxins	Pericardial rub
	15. Neurological	Uremic toxins, Aluminum toxicity, HTN	Headache, poor concentration, seizure Neuropathy, myopathy, depression, te
Metabolic	16. GIT (Gastritis, peptic ulcer)	Uremic toxins	Abdominal pain, GERD, Hematemes
	17. Glucose intolerance	Tissue insulin resistance	Lab: ↑↑ glucose
	18. Hyperlipidemia	Lipoprotein lipase	Lab: ↑↑ lipids

## Pathogenesis (CRF is a *Progressive* disease)

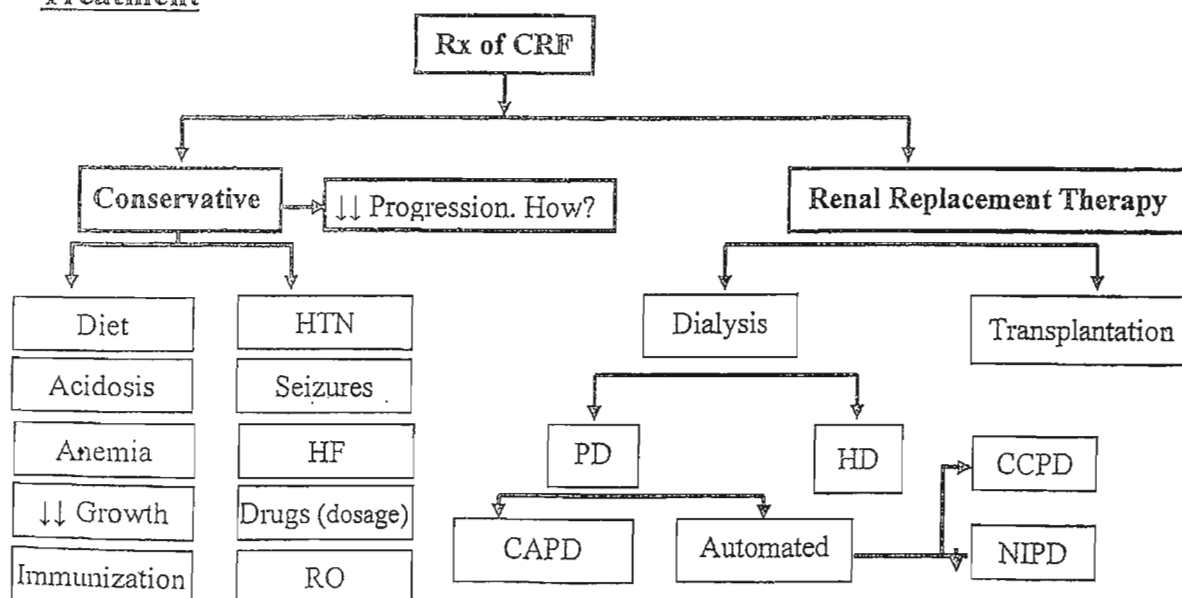
Mechanisms of progressive renal impairment	Slowing the rate of progression
<ol style="list-style-type: none"> <li>1. <b>Hyperfiltration injury</b> (<math>\uparrow\uparrow</math> GFR per Nephron)  <math>\uparrow\uparrow</math> Filtration through the remaining healthy nephrons (<i>although compensatory</i>) is injurious  <math>\rightarrow</math> more nephrons (Vicious cycle)</li> <li>2. <b>Proteinuria</b> (Direct toxic effect)</li> <li>3. <b>Hypertension</b> (<math>\uparrow\uparrow</math> Filtration &amp; arteriolar <math>\Delta</math>)</li> <li>4. <b>Hyperphosphatemia</b>: <math>\uparrow\uparrow</math> Ca x P product <math>\rightarrow</math> Metastatic calcification</li> <li>5. <b>Hyperlipidemia</b></li> <li>6. <b>Anemia</b></li> <li>7. <b>Immunologic injury</b> (Persistent inflammation)</li> <li>8. <b>Drugs</b></li> <li>9. <b>Dehydration</b></li> <li>10. <b>UTI &amp; Obstructive uropathy</b></li> </ol>	<ol style="list-style-type: none"> <li>1. <b>ACE inhibitors or ARB</b> (e.g., Captopril...) <ul style="list-style-type: none"> <li>▫ VD of the efferent &gt; afferent arteriole</li> <li>▫ <math>\downarrow\downarrow</math> Glomerular capillary hydrostatic P</li> <li>▫ <math>\downarrow\downarrow</math> Hyperfiltration,</li> <li>▫ <math>\downarrow\downarrow</math> BP, <math>\downarrow\downarrow</math> proteinuria</li> </ul> </li> <li>2. <b>Control of hypertension</b> (&lt; 75<sup>th</sup> %)</li> <li>3. <b>Control of hyperphosphatemia</b> (Ca x P &lt; 55)</li> <li>4. <b>Control of hyperlipidemia</b></li> <li>5. <b>Control of anemia</b> (r-HuEPO)</li> <li>6. <b>Control of hyperlipidemia</b></li> <li>7. <b>Avoid nephrotoxic drugs</b> (NSAIDs)</li> <li>8. <b>Avoid dehydration</b></li> <li>9. <b>Control of UTI &amp; obstructive uropathy</b></li> <li>10. <b>Prevention of obesity &amp; smoking</b></li> </ol>

## Investigations

- KFTs (Creatinine & urea). Estimation of GFR (*Schwartz formula*)
- Electrolytes: Na ( $\uparrow\uparrow$  or  $\downarrow\downarrow$ ),  $\uparrow\uparrow$  K
- Normal or  $\downarrow\downarrow$  Ca,  $\uparrow\uparrow$  PO<sub>4</sub>,  $\uparrow\uparrow$  Alkaline phosphatase (hyperphosphatasia),  $\uparrow\uparrow$  PTH
- Blood gases: metabolic acidosis
- CBC: anemia
- Urinalysis: may show proteinuria, hematuria or pyuria. Low fixed specific gravity
- CXR: cardiomegaly & pulmonary congestion ( $\pm$  APE)
- Left wrist X-ray: for bone age (delayed)
- Long bones: rachitic changes & subperiosteal erosions (phalanges)
- Renal US: usually small, echogenic with lost cortico-medullary differentiation
- Echocardiography: cardiomyopathy (uremic) & LV hypertrophy (HTN)
- ECG:  $\uparrow\uparrow$  K  $\rightarrow$   $\uparrow\uparrow$  PR, wide QRS,  $\uparrow\uparrow$  T (tall peaked T wave)
- Investigation of the cause (ANA, Anti DNA Ab, C<sub>3</sub>, C<sub>4</sub>, ESR...)
- Renal biopsy may show picture of the cause only *early* in the disease

$$\text{GFR} = \frac{\text{K} \times \text{Height (cm)}}{\text{Serum creatinine}}$$

## Treatment





## D) Conservative Treatment

### 1. Diet:

- Caloric intake: should be at RDA (recommended daily allowance)
- CHO & fats: unrestricted amounts
- Proteins: 2.5 g/Kg/day of high biological value (meat, eggs, fish )
- Supplementation of water soluble vitamin: specially B<sub>6</sub>, folic acid
- Fluid: restriction is rarely needed (except in ESRD)
- Na: Restriction in HTN & HF  
Supplementation in polyuria (Tubulointerstitial disease)
- Potassium: ↓↓ K intake (citrus fruits, bananas)  
Oral Na polystyrene sulfonate (Kayexalate)

### 2. Acidosis: NaHCO<sub>3</sub>

### 3. Anemia:

- Recombinant human erythropoietin [r-HuEPO]: 50-150 units/kg SC 1-3 times/wk  
It is indicated when Hb < 10g%
- Packed RBC (↓↓ Success of renal transplantation due to sensitization)
- Dialysis or renal transplantation

Benefits	Potential Complication
Avoid blood transfusions	Iron deficiency ( <i>IV or oral Iron is needed</i> )
↓↓ Sensitization to HLA antigens	Hypertension
↓↓ Exposure to infectious disease	Seizures
↑↑ Appetite	Pure red cell aplasia
↑↑ Exercise tolerance, activity, well-being	Clotting of vascular access

### 4. HTN

- Salt & fluid restriction and diuretics (Frusemide)
- ACE inhibitors (captopril) or angiotensin receptor blockers "ARB" (e.g., Losartan)
- Ca channel blockers (Nifedipine) 0.5-3 mg/Kg/day
- Hydralazine IV (0.1-0.5 mg/Kg/dose)
- Propranolol (0.5-4 mg/Kg/day)
- Na nitroprusside (not used due to thiocyanate toxicity)

### 5. Seizures

- Rx of the cause (↓↓ Na & ↓↓ Ca)
- Diazepam 0.3-0.5 mg/Kg/dose

### 6. HF

- Salt & fluid restriction and diuretics (Frusemide)
- ACE inhibitors (Captopril)
- Control of HTN & anemia
- Digitalis (the dose should be adjusted)

#### Causes of Anemia in CRF:

1. ↓↓ Erythropoietin (most important)
2. ↓↓ iron utilization
3. ↓↓ RBC life span (# of Na-K ATPase)
4. ↓↓ intake: anorexia & vomiting
5. Dilutional anemia
6. Bleeding tendency (Thromocytopathy)
7. Bleeding: sampling, insertion of VA
8. VA related complications
9. Residual blood in HD machine circuits
10. Hemodialysis (loss of folic acid)

### 7. Growth failure

- Adequate caloric intake
- Correction of anemia, acidosis, RO & initiation of dialysis when needed
- Recombinant human GH (rHuGH): Patients with CRF have GH resistance (↑↑ GH & ↓↓ IGF-1), so pharmacologic doses are needed

### 8. Drug dosage (for drugs with renal metabolism) either by ↓↓ dose or ↑↑ interval

### 9. Immunization: Routine vaccines + Influenza vaccine

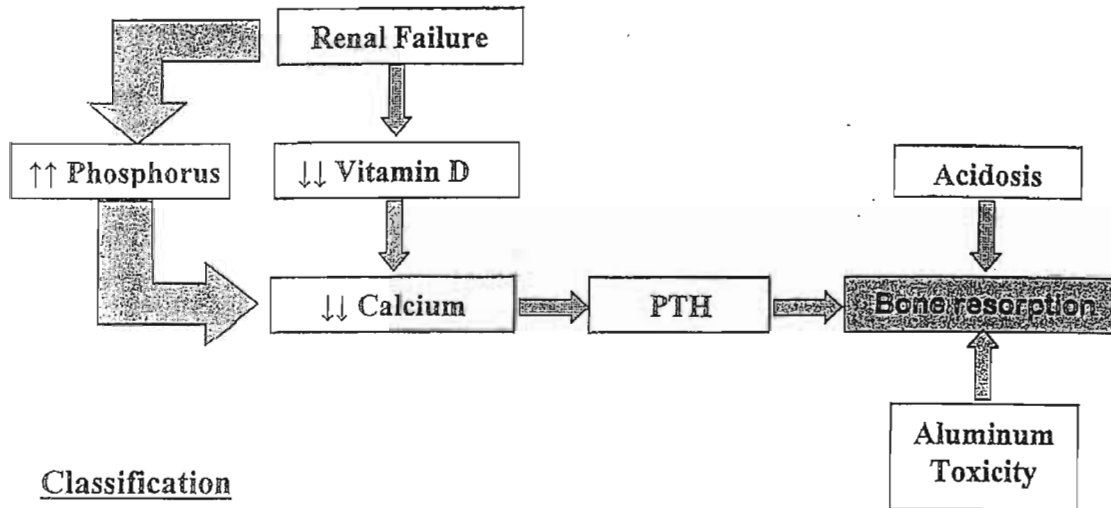
### 10. Renal Osteodystrophy

## Renal Osteodystrophy

### Definition

It is the full spectrum of bone disorders seen in patients with CKD

### Pathophysiology



### Classification

- ☑ **High-turnover bone disease**  
Cause: Secondary hyperparathyroidism  
Pathology: Osteitis fibrosa cystica
- ☑ **Low-turnover bone disease (adynamic)**  
Cause: Oversuppression of PTH (use of Ca containing PO<sub>4</sub> binders and vitamin D)  
Pathology: osteomalacia
- ☑ **Mixed lesions**

### Clinical Picture

- Muscle weakness
- Bony pain, pathological fractures
- Rickets, deformities (varus & valgus)

### Investigations

- ↑↑ PO<sub>4</sub>, ↓↓ Ca, ↑↑ alkaline phosphatase
- ↑↑ or normal PTH
- X-rays: ↓↓ bone age, subperiosteal bone resorption, rickets, deformities, fractures

### Treatment

- a. **Dietary phosphate restriction:** Milk, cheese, yogurt  
Use low PO<sub>4</sub> formula in infants e.g., Similac PM 60/40
- b. **Phosphate binding agents**  
Sevelamer (*Renagel*), Ca carbonate, Ca acetate taken with meals. Aluminum-containing binders "Mucogel" *should be avoided* (Aluminum toxicity: bone & CNS)
- c. **Vitamin D therapy:** indicated if ↑↑ PTH > 3 folds & in persistent hypocalcemia
  - ☑ **Calcitriol** (1,25 dihydroxycholecalciferol): 0.01-0.1 µg/Kg/day (max: 2 µg/day)
  - ☑ **1α hydroxycholecalciferol:** 0.05-0.1 µg/Kg/day
- d. **Parathyroidectomy:** Considered in severe cases not responding to Rx with vitamin D
- e. **Correction of metabolic acidosis**
- f. **Renal replacement therapy** (Dialysis or RT)

Ca x PO<sub>4</sub> product should be < 55 to prevent tissue deposition

## II) Renal Replacement Therapy (*Indicated in ESRD*)

### Indications

- CKD 4
- Refractory fluid overload
- Refractory electrolyte disturbances
- Acidosis
- Growth failure
- Uremic symptoms: Fatigue, nausea, impaired school performance...

### Method

- The ultimate **goal** is successful renal **transplantation**
- Dialysis is a just a "**bridge**" to RT
- Choice of modality of dialysis should be "individualized"
- 88% of children < 5 yrs are treated with PD
- 55% of children > 12 yrs are treated with HD

### A) Dialysis

#### 1. Peritoneal Dialysis

**Technique** (see before)

**Catheter:** Surgically inserted catheter (**Tenckhoff** catheter)

**Types:** Continuous ambulatory PD

Automated (using **cyclers**): Continuous cyclic PD (CCPD)

Nocturnal intermittent PD (NIPD)

<b>Advantages</b>	<b>Disadvantage</b>
Can be done at home	Catheter malfunction (Obstruction, kinking)
Free daily activities (school)	Catheter-related infections (peritonitis, exit site)
Technically easier ( <i>than HD</i> )	↓↓ Appetite
Less expensive ( <i>than HD</i> )	Impaired body image & hernia
Independence ( <i>Adolescents</i> )	Caregiver fatigue

#### 2. Hemodialysis

**Technique** (see before)

**Vascular access:**

- ☒ AV fistula
- ☒ AV graft
- ☒ Catheters (Internal jugular or subclavian)

## B) Renal Transplantation

### Types

- ☒ Living related
- ☒ Living non-related
- ☒ Cadaveric

### Contraindications

- Active infection
- Severe mental retardation
- Obstructive uropathy
- Cardiovascular or liver disease
- Massive obesity

### Clinical & Laboratory Evaluation

	Recipient	Donor
History	Complete history & physical examination	
	Immunization history	
Investigation	Blood group & HLA-A, B, C, DR + (cross matching) CBC, creatinine, electrolytes, LFTs, Blood glucose; Coagulation profile Urinalysis, urine culture, 24-hr urine proteins Hepatitis, CMV, EBV, Varicella CXR	
	C <sub>3</sub> , C <sub>4</sub> , ANA Neurological & Urological evaluation	Creatinine clearance ECG, renal US, IVP, renal angiogram

### Procedure

- Recipient's kidneys are usually left
- Children < 15-20 Kg → the kidney is placed intraperitoneal
- Children > 15-20 Kg → the kidney is placed retroperitoneal (Rt iliac fossa)
- Vascular anastomosis

### Immunosuppression

The most frequently used protocol is (Cyclosporine & low-dose steroids)

### Complications

- ATN, graft thrombosis
- Infections (CMV, EBV): Immunosuppressives → uncontrolled B-cell proliferation
- Post-transplantation lymphoproliferative Disorder (PTLD): EBV-related uncontrolled B-cell proliferation → lymphadenopathy, GIT (mass, bleeding, obstruction), CNS (seizures)
- Malignancy
- Recurrence of the original disease (e.g., FSGS, MPGN type II)
- Rejection:
  - ☒ Immune-mediated (cell-mediated & humoral-mediated)
  - ☒ More in cadaveric RT
  - ☒ Onset: hyperacute, acute or chronic
  - ☒ C/P: Fever, anorexia, oliguria, HTN, graft swelling & tenderness
  - ☒ Investigation: ↑↑ KFTs, U/S (swollen, echogenic), biopsy (Lymphocytic infiltration)
  - ☒ Rx: immunosuppressives

### Prognosis → Living Related Donor

- LRD → 5 yr graft survival is 80%
- Cadaveric → 5 yr graft survival is 65%

# Urinary Tract Infection

## Definition

It is growth of bacteria in the urinary system

Urine in normal UB is sterile

## Epidemiology

- It is a common pediatric infection affecting 5% of all children
- ♂:♀ = 3:1 (1<sup>st</sup> year)  
1:10 (>1 yr)

UTI in the pediatric age group is a well recognized cause of:  
 ➤ Acute morbidity  
 ➤ HTN, renal insufficiency

## Etiology

- E.coli\*\* (most common ≈ 80 %)
- Klebsiella
- Proteus: Splitting of urea to ammonia → Urine alkalinisation & PO<sub>4</sub> stones
- Pseudomonas: Indicates the presence of urinary tract structural abnormality
- Others: Staphylococci, Streptococcus fecalis, GBS, Adenovirus

## Pathogenesis

### a. Route of infection:

- Ascending\*: most common
- Blood-borne: neonatal period

Frequent & complete UB emptying is a strong protective factor

### b. Bacterial virulence: fimbriae "Type I & type II" (bacterial adherence to mucosal cells)

### c. Host factors

- Uncircumcised ♂ (10-20 folds)
- ♀ sex (short urethra)
- Obstruction (PUV, PUJ, UVJ, stones)
- Toilet training
- Voiding dysfunction
- Constipation
- Enterobius
- VUR (present in 1/3 of patients with UTI)
- Neurogenic bladder
- Malformation (ectopic ureter)
- Wiping from back to front (in ♀)
- Poor hygiene
- Sexual activity
- Bubble baths

## Pathology & Classification

### A. Cystitis: Mucosal congestion + Detrusor muscle hyperactivity

- Acute hemorrhagic cystitis: caused by E.coli or adenovirus
- Eosinophilic cystitis: ?allergic, UB masses, obstructive uropathy, DD: malignancy
- Interstitial cystitis: Idiopathic bladder ulcers "commonly in adolescent ♀"

### B. Pyelonephritis

- Pyelonephritis: Involvement of the renal parenchyma
- Pyelitis: No involvement of the renal parenchyma
- Acute lobar nephronia: Acute focal infection with formation of a mass
- Xanthogranulomatous pyelonephritis: Giant cell & histiocytes

### C. Asymptomatic Bacteriuria

- Positive urine culture WITH NO manifestations
- Most common in ♀
- Benign with no renal damage

## Clinical picture

### A) Pyelonephritis:

#### a. Newborns & Young Infants: "Non-specific symptoms"

- Fever\* (Temperature instability)
- Vomiting & Diarrhea
- FTT
- Abdominal distension
- Feeding difficulties
- Jaundice (Cholestasis)
- Irritability
- Sepsis

#### b. Older children:

- Fever\* & Chills
- Flank pain & tenderness
- Nausea, vomiting & diarrhea

Renal scar occurs in 30-50% of PN  
Early Rx ↓↓ risk of scarring

UTI should be considered in any infant  
with **unexplained fever**

### B) Cystitis:

- Dysuria
- Urgency (*Intense desire*)
- Frequency
- Incontinence (*urine leakage*)
- 2ry enuresis
- Suprapubic pain
- Malodorous urine (*Not specific*)

No fever  
No renal injury

## Investigations

### A) Laboratory

Urine culture is essential  
for diagnosis & TTT

The correct diagnosis depend on having a proper urine sample

#### Methods of urine collection:

- ☑ Midstream urine collection: in toilet-trained children
- ☑ Urine bag: Non-invasive, ↑↑ risk of contamination, Good -Ve test (rule out UTI)
- ☑ Bladder catheterization
- ☑ Suprapubic aspiration: Generally not necessary

#### a. Urine analysis:

- ▣ Pyuria (Pus cells > 5/HPF) is suggestive of UTI
- ▣ WBC casts
- ▣ Nitrites
- ▣ Leukocyte esterase
- ▣ ↑↑ Epithelial cells is an index of possible contamination

#### Sterile Pyuria:

1. Antibiotics
2. Viral infection
3. TB
4. Obstructive uropathy
5. STI
6. TIN
7. Collagen-vascular
8. Fever & dehydration

False Positive (Pyuria without UTI)	False Negative (UTI without pyuria)
Fever & dehydration	Antibiotics therapy
Nephritic syndrome (PSGN)	TB, viruses
Other causes of sterile pyuria	Closed infection (Obstructive uropathy)

**b. Urine Culture:**

Method	Significant Colony Count
Midstream urine collection	>100,000 single pathogen
	>10,000 single pathogen + symptoms
UB catheterization	>1,000 single pathogen
Suprapubic aspiration	Any number

Refrigeration is a reliable method of storing urine till it can be cultured

**c. Others**

- CBC: Leukocytosis & neutrophilia in pyelonephritis
- ESR & CRP
- Blood culture is indicated in neonates & infants (sepsis is common)

**B) Imaging****Aim of Imaging Studies:**

- ☐ Identification of anatomical abnormalities
- ☐ Determination of any renal involvement
- ☐ Assessment of renal function

**Available Options:****1. Renal scan (DMSA)**

- Diagnosis of pyelonephritis (↓↓ Uptake + normal volume)
- Detection of renal scarring (↓↓ Uptake + ↓↓ volume)
- 50% of children with febrile UTI have positive DMSA
- If DMSA is negative during attack of febrile UTI, there is no risk of renal scarring

**2. U/S**

- Indications:
  - First episode of clinical pyelonephritis
  - Frequently occurring lower UTIs
- Value:
  - Renal size, echogenicity & C/M differentiation
  - Diagnosis of obstructive uropathy (hydronephrosis & hydronephrosis)
  - Detection of renal scarring

**3. VCUG (*Indications are controversial & changing*)**

- Indications:
  - Febrile UTI with abnormal renal scan (DMSA)
  - AAP (1990) recommended US & VCUG for all infants with febrile UTI... "rewritten"
  - NICE guidelines (2007) recommended VCUG in infants < 6 months
- Value:
  - Diagnosis & grading of VUR
  - Diagnosis of PUV, neurogenic UB,
- Types:
  - Radiographic VCUG: can visualize the urethra (important in ♂, why?)
  - Radio isotopic VCUG: does not visualize urethral anatomy (can be used in ♀)

**4. CT & MRI****5. IVP: No longer used in evaluation (↑↑ radiation dose & contrast-related allergic reactions)**

## Treatment

### A) Acute Cystitis

- Route: Oral antibiotics
- Duration: 3-5 days
- Drugs
  - Sulfamethoxazole-Trimethoprim (SMZ = 20 mg/Kg/day, TMP = 4 mg/Kg/day)
  - Nitrofurantoin (5-7 mg/Kg/day)
  - Amoxicillin (50 mg/Kg/day)

Treatment should be **started** without delay then **modified** according to the result of culture

### B) Acute Pyelonephritis

- Route: Parenteral (± Oral) antibiotics
- Duration: 10-14 days
- Drugs
  - Ceftriaxone (50-75 mg/Kg/day) or
  - Cefotaxime (100 mg/Kg/day)
  - Ampicillin (100 mg/Kg/day) + Aminoglycoside (Gentamicin 3-5 mg/Kg/day) or
  - IM Ceftriaxone followed by oral therapy (Cefixime) or
  - Ciprofloxacin: in patients > 17 yrs

#### **Indications of admission:**

1. Neonates
2. Toxic children
3. Vomiting & Dehydration

	<b>Cystitis</b>	<b>Pyelonephritis</b>
<b>Drugs</b>	Co-trimoxazole Or Nitrofurantoin (5-7 mg/Kg/day) Or Amoxicillin (50 mg/Kg/day)	Ceftriaxone (50-75 mg/Kg/day) Or Cefotaxime (100 mg/Kg/day) Or Gentamicin (4 mg/Kg/day) + Ampicillin (100 mg/Kg/day) Or Oral 3 <sup>rd</sup> gen. cephalosporin (Cefixime)
<b>Route</b>	Oral	IV for 5 days then oral
<b>Duration</b>	3-5 days	10-14 days

- ☐ Urine culture should be done 1 week after termination of Rx
- ☐ Urine culture during Rx is invariably negative

### C) Surgical Rx in case of pyonephrosis

### D) Treatment of predisposing factors: VUR, Obstructive uropathy, voiding dysfunction

### E) Antibiotic Prophylaxis

- Indication: VUR, obstructive lesions, neurogenic bladder, urinary tract stasis
- Route: Oral antibiotics
- Dose: 1/3 therapeutic dose once daily
- Duration: long-term (or till resolution of indication)
- Drugs: SMZ-TMP, Nitrofurantoin, Amoxicillin (In infants < 2 months), Cephalexin

### F) Other Lines

- Adequate fluid intake
- Frequent voiding
- Ensuring complete bladder emptying (a second time to empty bladder after a minute)
- Avoid constipation
- Lactobacillus acidophilus (probiotic): Replaces pathogenic bacteria (prevention of UTI)
- Cranberry juice: prevents bacterial adhesion



# Vesico-Uretral Reflux

## Definition

Retrograde flow of urine from UB upwards toward the kidney

## Classification

- A) **Primary:** Congenital anomaly at the uretero-vesical junction (? Genetic)  
 B) **Secondary:** High pressure voiding (PUV, neurogenic bladder, voiding dysfunction...)

## Clinical Picture

Recurrent UTI

## Complications

Renal scarring, CRF, HTN

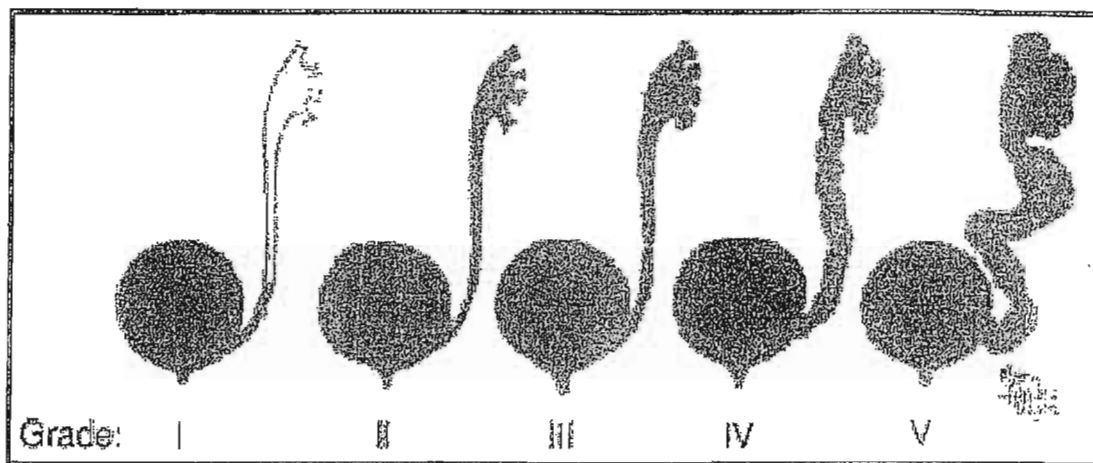
- Reflux nephropathy: Reflux-related renal injury
- CRF, HTN

Sterile VUR in the absence of ↑↑ UB pressure does not cause renal damage

80% of low-grade VUR resolve over time

## Investigations

VCUG



## Treatment

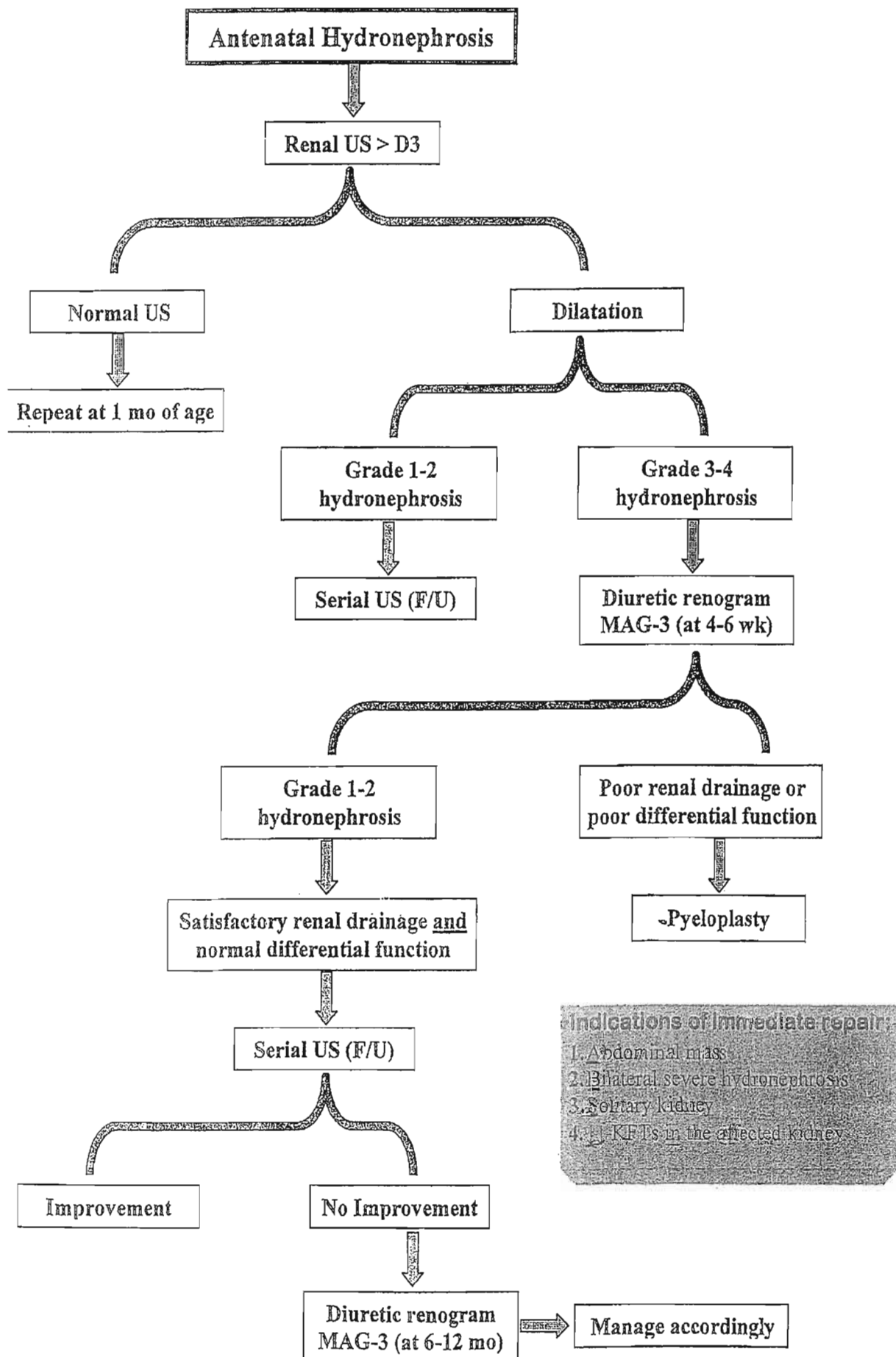
(Rx of the cause in 2ry VUR)

D) **Prophylaxis:** See before

E) **Surgery** (Uretric reimplantation or endoscopic correction):

- Failure of medical Rx: Breakthrough UTI or Persistent VUR
- High grade VUR that are unlikely to resolve spontaneously

Grade	Description	Treatment
I	VUR into a non-dilated lower ureter	Medical Rx (Antibiotic Prophylaxis)
II	VUR into a non-dilated ureter & renal pelvis	
III	VUR into a mildly dilated ureter	0-5 yrs: Medical (Antibiotic prophylaxis); 5-10 yrs: Surgery
IV	VUR into a grossly dilated ureter	
V	VUR into a dilated tortuous ureter + Lost papillary impression	Surgery after the 1 <sup>st</sup> year



## Nocturnal Enuresis

### Definition

It is involuntary voiding of urine during sleep after the expected age of control ( $\approx 5$  yrs)

Nocturnal enuresis may be:

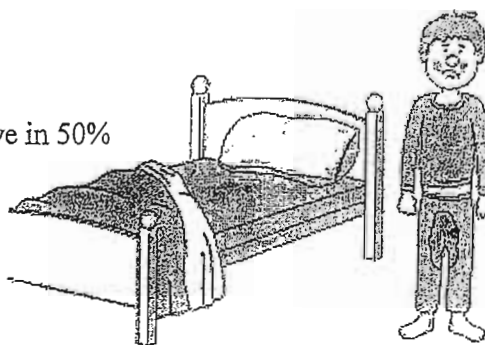
- a. **Primary** or secondary [1ry = No dry period before]  
[2ry = Dry period  $\geq 6$  months before]
- b. **Mono-** or **Non-monosymptomatic** [Mono- = Only bed wetting]  
[Non- = Other symptoms; UTI, frequency, urgency...]

### Incidence ♂:♀ = 3:1)

- 5 yrs: 10%
- 10 yrs: 5%
- 12 yrs: 3%
- 15 yrs: 1%

### Etiology (Multifactorial)

1. **Delayed maturation** of central voluntary control
2. **Sleep disorder** (deep sleepers)
3. Sleep apnea (**adenoids**)
4.  $\downarrow\downarrow$  **ADH production** at night (Nocturnal polyuria)
5. **Genetic factors** (12 & 13q): Family history is positive in 50%
6. **Organic cause** (UTI, Obstructive uropathy)
7. Causes of **polyuria** (DM, DI, CRF)
8. **Psychological factors** (Divorce, child birth, abuse)



### Evaluation

- Urinalysis: Pyuria, glucose, specific gravity
- Urine culture
- Renal US: In older children or resistant cases

### Treatment

- A) **General Measures & Motivational:** [Success rate = 30%]
  - a.  $\downarrow\downarrow$  Fluid intake in the evening & ?  $\downarrow\downarrow$  intake of cola, chocolate & citrus products
  - b. Urination before sleep
  - c. Waking the child few hours after sleep to void (*using clock alarm*)
  - d. Rewarding for dry nights (Star chart for dry nights)
  - e. Avoid punishment
  - f. Reassurance (common condition - spontaneous resolution 15-20% / yr)
- B) **Rx of the cause:** Adenoidectomy, UTI...
- C) **Bladder exercise:** No evidence of its efficiency
- D) **Enuresis alarms (Conditioning therapy)** [Success rate = 30-60%]  
Auditory or vibratory alarm is attached to a wetness sensor in the underwear
- E) **Medications**

	Action	Dose	Side effects	Success
<b>Desmopressin</b> ( <i>Minirin</i> )	Synthetic ADH analogue	0.2-0.6 mg 1 hr before bed time for 3-6 months (then tapering)	Hyponatremia	40%
<b>Imipramine</b> ( <i>Tofranil</i> )	Anti-cholinergic Alter sleep cycles	25-50 mg 1 hr before bed time	Arrhythmias Anxiety Insomnia Dry mouth	30-60%
<b>Oxybutynin</b> ( <i>Uripan</i> )	Anti-cholinergic	5 mg at bed time	Short action (6 hours)	Low

# Voiding dysfunction

## Normal Voiding & Toilet training

**Fetal life:** Reflex UB contraction

**Toilet training:** Can be started at the age of 2-4 yrs

**Girls** acquire bladder control before boys

**Bowel** control is achieved before bladder control

**By 5 yrs:** 90% are dry during the day, 80% are dry at night

## Sequence of control:

1. Bowel control at night
2. Bowel control during the day
3. Urine control during the day
4. Urine control at night

## Diurnal Incontinence

(Daytime Wetting)

### Definition.

It is involuntary leakage of urine during waking hours after the expected age of control ( $\approx 5$  yr)

### Incidence

- 5-10% of children aged between 5-10 yrs
- More common in ♀

### Etiology%

Organic causes  
Psychological  
Special

#### A) Organic causes:

1. UTI: with all predisposing factors
2. Urethritis: bubble bath, FB
3. Neuropathic: Neural tube defect (Tethered spinal cord...)
4. Ectopic ureter (*Ureter is inserted in the vagina  $\rightarrow$  continuous dribbling*)
5. Polyuria (DM, DI, RTA...)

#### B) Psychological causes:

1. Stress-related: loss of a parent, divorce, abuse
2. Resistive child (reaction to punishment)

#### C) Special types:

1. Pediatric Unstable Bladder (Overactive bladder): Most common
2. Non-neurogenic neurogenic Bladder (Hinman)
3. Infrequent Voiding (*Lazy UB*)
4. Vaginal Voiding
5. Giggle Incontinence (*Incontinence with giggling*)

### Evaluation

#### A) History:

- General history: Fever, bowel habit, abuse...
- Voiding history: Frequency & timing of wetting (continuous or intermittent), volume  
Desire to micturition, hold maneuvers, straining, urine stream, dysuria
- Psychological history: Family attitude, stresses...

#### B) Examination:

- Abdominal examination: UB mass, fecal masses
- Back: Lipoma, dimple, sinus, tuft of hair (*occult neurological lesion*)
- Genital examination: sexual abuse, urethral lesion, perineal sensation, PR (rectal tone)

### C) Investigation:

- Urinalysis & culture
- Imaging according to the suspected cause (US, VCUG, MRI spine...)
- Urodynamic study

### Treatment

1. Timed voiding at 1-2 hour interval
2. Biofeedback: Bladder exercises (Bladder stretching & stream interruption exercises)
3. Psychological & motivational
4. Medications: Oxybutynin is used in unstable bladder & Hinman syndrome

#### **Overactive (Unstable) Bladder**

**Etiology:** Functionally smaller UB  
Uninhibited strong UB contraction  
**C/P:** Frequency, urgency, incontinence,  
Vincet's curtsy (squat to prevent leakage)  
**Natural history:** Resolution is the rule  
**Rx:** Timed voiding  
Oxybutynin

#### **Non-neurogenic neurogenic Bladder (Hinman syndrome)**

**Etiology:** Detrusor-sphincter dyssynergia  
(Failure of relaxation of the ex. sphincter)  
**C/P:** Staccato stream, incontinence, UTI  
**Investigation:** VUR, hydronephrosis (severe cases)  
**Rx:** Timed voiding (CIC)  
Oxybutynin  
Botulinum toxin (Botox)

#### **Vaginal Voiding**

**Etiology:** Labial adhesions  
Lack of leg separation during urination  
**C/P:** Incontinence after urination on standing up  
**Rx:** Proper leg separation  
Pulling the child's underwear down  
Estrogen creams for labial adhesions

#### **Infrequent Voiding**

**Etiology:** Child voids once/ twice daily  
Behavioral  
**C/P:** UTI (due to retention) ± incontinence  
**Rx:** Frequent voiding  
Rx of UTI

## Renal Cysts

### Etiology

#### A) Genetic:

- Autosomal recessive polycystic kidney disease (ARPKD)
- Autosomal dominant polycystic kidney disease (ADPKD)
- Juvenile nephronophthisis (NPH)
- Medullary/cystic kidney disease (MCKD)
- Glomerulocystic kidney disease (GCKD)

#### B) Developmental

Multicystic dysplastic kidney (MCDK)

#### C) Systemic diseases

- Tuberous sclerosis (TS)
- Von Hippel-Lindau syndrome (VHLS)
- Zellweger syndrome
- Laurant-Moon-Biedl syndrome

#### D) Acquired

- Simple cysts
- Medullary sponge kidney (Hypercalciuria, nephrocalcinosis, stones, RTA)

## ARPKD & ADPKD

	ARPKD (Infantile)	ADPKD (Adult)
Genetics	AR <sup>o</sup>	AD <sup>16</sup>
Incidence	1:10,000	1:1000
Pathology	Renal enlargement Microscopic cysts Cysts are dilatation of the collecting tubules Liver: periportal fibrosis (100%) = CHF Bile duct proliferation & Caroli's disease	Renal enlargement Larger cysts Cysts develop from all nephron regions
Affected Organs	Kidneys & Liver only	Kidneys & Extra-renal (Liver, brain, GIT)
Clinical Picture	<p><i>Depends on the age of onset:</i></p> <p><b>A) Fetal:</b> Oligohydramnios</p> <p><b>B) Neonatal:</b></p> <ul style="list-style-type: none"> <li>▣ Bilateral flank masses</li> <li>▣ Pulmonary hypoplasia (RD)</li> <li>▣ Potter facies: flat nose, micrognathia, low-set ears, limb-positioning defects</li> <li>▣ HTN, renal failure</li> </ul> <p><b>C) Infantile</b></p> <ul style="list-style-type: none"> <li>▣ Renal failure</li> <li>▣ HSM</li> </ul> <p><b>D) Childhood</b></p> <ul style="list-style-type: none"> <li>▣ HSM, portal hypertension, GIT bleeding (hematemesis &amp; melena), hypersplenism</li> <li>▣ CRF</li> </ul>	<p>May be asymptomatic</p> <ul style="list-style-type: none"> <li>▣ Onset: 30-50 yrs (may in neonates)</li> <li>▣ Hematuria</li> <li>▣ Flank pain, flank masses</li> <li>▣ HTN</li> <li>▣ Extrarenal manifestations:               <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Intracranial aneurysms, SAH</li> <li><input checked="" type="checkbox"/> Hepatic cysts</li> <li><input checked="" type="checkbox"/> Intestinal diverticuli</li> <li><input checked="" type="checkbox"/> Mitral valve prolapse</li> </ul> </li> <li>▣ ESRD (50-70 yrs)</li> </ul>
Prenatal Diagnosis	Available	
Diagnosis	<ul style="list-style-type: none"> <li>▣ Lab: KFT, electrolytes, LFT, CBC</li> <li>▣ U/S (markedly enlarged, echogenic, poor C/M differentiation, No cysts ...)</li> <li>▣ Invasive: Liver &amp; Renal biopsy Upper GIT endoscopy</li> </ul>	<ul style="list-style-type: none"> <li>▣ Lab: KFT, electrolytes, LFT, CBC</li> <li>▣ U/S (enlarged kidneys, macrocysts ...)</li> <li>U/S may be normal in 20% by 20 yrs</li> <li>▣ Invasive: Renal biopsy</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>▣ Supportive (HTN, fluid ...)</li> <li>▣ Respiratory care (<i>mechanical ventilation</i>)</li> <li>▣ Renal replacement therapy (Dialysis, RT)</li> <li>▣ Liver support</li> </ul>	<ul style="list-style-type: none"> <li>▣ Supportive</li> <li>▣ Control of HTN (ACE inhibitors*)</li> <li>▣ Renal replacement therapy</li> </ul>
Prognosis	Neonatal mortality = 30% >50% develop ESRD during the 1 <sup>st</sup> decade	Neonatal 50% develop ESRD at 50-70 yrs

# Urinary Lithiasis

(Calculi- Stones)

## Incidence%

Urinary stones are now diagnosed with increasing frequency in children

## Etiology

### A) Metabolic:

1. Hypercalciuria
2. Hyperoxaluria
3. Hyperuricosuria
4. Cystinuria
5. Xanthinuria
6. Orotic aciduria
7. Hypocitraturia (RTA type I, malabsorption)

B) Anatomical anomalies: Obstructive uropathy

C) Infection: by urea-splitting organisms (*Proteus*\*)

D) Idiopathic

## Pathogenesis

1. ↑↑ Urinary solute: (causes = 1-6)
2. ↓↓ Urinary Inhibitors: Citrate, Mg, diphosphonate...
3. Urine Stasis
4. Urine pH: e.g., Uric acid (pH = 6-7)

## Clinical picture

- Accidentally discovered
- Pain, hematuria, UTI, retention, post-renal ARF, CRF

## Investigations

### A) Laboratory

- Urine analysis, urine culture
- Urine pH, Ca, PO<sub>4</sub>, oxalate, cystine, uric acid, citrate, creatinine
- Blood Na, K, Ca, PO<sub>4</sub>, alkaline phosphatase, uric acid, ABG, BUN, creatinine
- Stone analysis (after surgical removal or spontaneous passage)

### B) Imaging

- PUT: Radio-opaque (Ca containing stones, infective stones, cystine)  
Radio-lucent (Uric acid, xanthine, orotic acid)
- U/S
- Spiral CT Most accurate
- IVP: rarely used in children

## Treatment

### A) Medical Rx

- ↑↑ fluid intake
- ↓↓ Dietary Na, Ca & protein (to RDA)
- B<sub>6</sub> (Hyperoxaluria)
- Alkalinization of urine (Uric & Cystine)
- Rx of UTI
- Thiazides (hypercalciuria)
- Penicillamine (cystinuria)
- Citrate (hypocitraturia & hypercalciuria)
- Allopurinol (Uric & Xanthine)

B) Surgery (Nephrostomy, ureteric stent to relieve obstruction, open lithotomy)

C) Extracorporeal Shock Wave Lithotripsy (ESWL)

### Hyperoxaluria:

#### 1. Primary (Genetic):

- Type I: ↓↓ Alanine glyoxylate aminotransferase
- Type II: ↓↓ D glycerate dehydrogenase

#### 2. Secondary

- ↑↑ Dietary oxalates
- ↓↓ B<sub>6</sub>
- Enteric hyperoxaluria (IBS, resection...)

### Hyperuricosuria:

#### 1. Tumor lysis syndrome

#### 2. GSD type 1

3. ↓↓ Hypoxanthine-guanine phosphoribosyl transferase (HPRT);
- Partial
- Complete (= Lesch-Nyhan syndrome)

### Stone formation:

1. Matrix
2. Precipitation-crystallization
3. Epitaxy
4. Inhibitors of stone formation

### Nephrocalcinosis:

Ca deposition within the renal tissue

# Renal Biopsy

## Definition

Renal tissue is obtained for histological & immunological examination

## Indications (Discuss)

1. Nephrotic syndrome	7. Lupus nephritis
2. PSGN	8. Recurrent gross hematuria
3. HUS	9. Persistent proteinuria
4. Membranous glomerulopathy	10. ARF
5. MPGN	11. CRF
6. RPGN	12. TIN

## Preparation

- ▣ Revise the indication
- ▣ Hb > 8 g%
- ▣ Platelets > 60,000/mm<sup>3</sup>
- ▣ PC > 60% (PT within 3 sec of normal)
- ▣ Abdominal US
- ▣ IV line
- ▣ Vitamin K
- ▣ Fasting for 2 hrs

## Contraindications

- ☒ Bleeding tendency
- ☒ Uncontrolled HTN
- ☒ Solitary kidney
- ☒ Suspected vascular, cystic or infectious lesions

## Methods

- ☒ Percutaneous\*\* (US guided)
- ☒ Laparoscopic
- ☒ Open (Laparotomy)

## Procedure

- US guided
- Conscious sedation ± LA
- The amount of tissue obtained is evaluated (Cortical tissue)

## Post-biopsy care

- Rest in bed
- Vital signs every 30 min (2 hrs), every 1 hr (2 hrs) the every 2 hrs
- If bleeding is suspected: IV fluids + Hb% + Hct ± blood transfusion + US

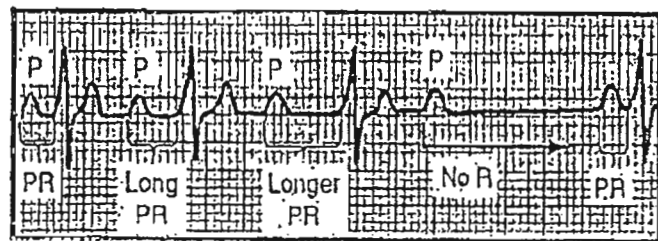
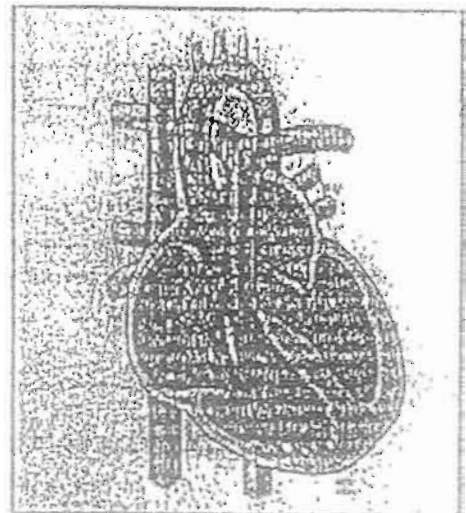
## Complications (Rare)

- Failure (Medullary tissue)
- AV fistula: hemorrhage
- Hemorrhage (Hematuria)
- Subcapsular & retroperitoneal hematoma
- Infection



## Examination (Discuss 3)





# Pediatric Cardiology

By

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2008

## Evaluation of the CVS

### A) History

- Antenatal history: Maternal DM, SLE, Congenital infection, Drugs. Why??
- Natal history: Prematurity, Obstructed labor, Cyanosis, RD.
- Onset of presentation: At birth, After few months
- Cardiac symptoms
  - Infants: Feeding pattern, Feeding difficulties, sweating
  - Older children: Exercise intolerance
  - Others: Chest pain...
- Family history: Relatives with CHD, Muscle weakness, early stroke or IHD

### B) Examination

- Other congenital malformations
- Anthropometric measurements: FTT
- Cyanosis
- Signs of HF: 3 T
- Peripheral pulses
  - Big pulse volume
  - Radio-femoral delay
  - Weak pulses
- Blood pressure: Auscultation, Palpation, Dinamap
- Cardiac examination
  - Combined inspection & palpation
  - Auscultation
  - ??Percussion: Almost obsolete

Ande edema commonly seen in adults is Not found in infants

Examination of JVP is of little use in infants

Pediatric patient sizes of cuffs: 3, 5, 7, 12, 18 cm

Auscultation is an ART that improves with practice

The absence of murmur does Not rule out significant CHD or acquired heart disease

### C) Investigation

1. CXR
  - Heart: Chamber enlargement
  - Chest: Lung vascularity
  - Chest infection
2. ECG
  - Chamber enlargement
  - Arrhythmias
  - Drug effects (Digitalis)
3. ECHO Cardiography & Doppler
  - Chamber enlargement
  - Cardiac structure
  - Cardiac contractility (FS %)
  - Valvular lesions
  - Septal defects
  - Intra-cardiac pressures, gradients & flow direction
  - Thrombi, Vegetations & Tumors
  - Assessment of coronaries
  - Pericardial effusion
4. MRI, MRA, CT, Cardiac (For evaluation of Pulm. VR)
5. Catheterization & Angiography
  - Diagnostic &/or Interventional
  - Pressure, O<sub>2</sub> saturation, abnormal tract, angiography

- In the term fetus RV = LV
- After birth the Rt ventricle ↓↓

"Cardiomegaly" on exp. films & thymus are common cause of unnecessary investigations!!

#### Digitalis Effect

- Sagging depression of ST
- Inverted or flat T-wave
- ↑↑ PR interval

#### Special ECHO

- Transesophageal ECHO (TEE)
- Fetal ECHO (17-19 wks)

#### Diagnostic Catheterization

- Complex CHD
- Proper estimation of P & BF
- Proper estimation of PVR
- Myocardial biopsy
- EPS

#### Interventional Catheterization

- Isolated Valvular AS or PS
- Balloon atrial septostomy (Rashkind procedure)
- Intravascular stents

## Cardiac Manifestations of Systemic Diseases

System	Pattern of cardiac involvement
<b>Hematologic disorders</b>	
Anemia	Tachycardia, High CO heart failure
Sickle cell anemia	Cardiomyopathy, High CO heart failure
Thalassemia	Cardiomyopathy, High CO heart failure
Hemochromatosis	Cardiomyopathy
DIC/Scpsis	Hypotension, Myocardial dysfunction
<b>Neuromuscular disorders</b>	
Friedreich's ataxia	Cardiomyopathy
Duchenne Dystrophy	Cardiomyopathy
Emery-Dreifuss	Cardiomyopathy??
Myotonic Dystrophy	Heart block & arrhythmias (Not cardiomyopathy)
Tuberous sclerosis	
Autonomic Neuropathy	HR & BP instability
<b>Mitochondrial Diseases</b>	
Kearns-Sayre	Heart Block
<b>Metabolic diseases</b>	
GSD II (Pompe)	Cardiomyopathy
Homocystinuria	Coronary thrombosis
MPS	AR, coronary artery disease
FA oxidation defects	Cardiomyopathy
Carnitine deficiency	Cardiomyopathy
<b>CT diseases</b>	
Marfan	AR, MR, Aortic dissection
Osteogenesis imperfecta	AR
Ehler-Danlos syndrome	Mitral valve prolapse
<b>Hepatic diseases</b>	
Liver cell failure	Hyperdynamic circulation, Porto-pulmonary shunts
Alagille syndrome	PS
<b>Endocrine diseases</b>	
Graves	Tachycardia, arrhythmia, big pulse volume & thyrotoxic crisis
Hypothyroidism	Bradycardia, pericardial effusion
Pheochromocytoma	Tachycardia, arrhythmia, HTN
<b>Rheumatic diseases</b>	
JRA	Pericarditis
SLE	Pericarditis, Libman-Sacks endocarditis, HTN, Congenital HB
Dermatomyositis	Cardiomyopathy, Conduction abnormalities
Scleroderma	Raynaud's, Systemic & pulmonary HTN, Restrictive cardiomyopathy
Kawasaki Disease	Coronary artery aneurysm
Amyloidosis	Cardiomyopathy
Vasculitis Syndromes	HTN, Cardiomyopathy
<b>Respiratory diseases</b>	
Suppurative lung & ILD	Pulmonary HTN, Cor-pulmonale
<b>Renal diseases (ARF &amp; CRF)</b>	Cardiomyopathy
<b>Genetics</b>	See below...

## Congenital Heart Diseases

### Incidence

- 8: 1000 of general population
- VSD is the most common (25-30%)

### Etiology

#### ☒ Genetic factors:

- Single gene defect: Marfan...
- Other congenital malformations
- Multifactorial

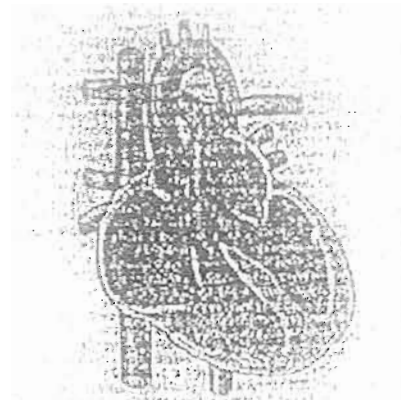
#### ☒ Environmental factors:

- Congenital infection (Rubella)
- Maternal drugs (Alcohol)
- Maternal diseases (DM)

Lesion	Frequency%
VSD	25-30
ASD	7
PDA	7
Coarctation	6
Fallot tetralogy	6
PS	6
AS	6
TGA	5
HLHS	2
Truncus arteriosus	1
Single ventricle	1
TAPVR	1
DORV	1
Tricuspid atresia	1

### Congenital Malformations Syndromes associated with CHD

Syndrome	Features
Trisomy-21	Endocardial cushion defects (AV canal), VSD, ASD
Trisomy-18	VSD, ASD
Trisomy-13	VSD, ASD
Cri-du-chat	VSD
Turner syndrome	CoA, Bicuspid aortic valve
Noonan	PS
Alagille's syndrome	PS
Cong. NS (Finish)	PS
DiGeorge Syndrome	Conotruncal anomalies (interrupted aortic arch, truncus arteriosus)
Kartaguer	Dextrocardia
Williams	Supravalvular AS
VATER/VACTERL	VSD, ASD, PDA
IDM	HCM, VSD
Maternal PKU	VSD, ASD, PDA
Fetal alcohol	VSD, ASD, PDA
Congenital Rubella	PDA
ADPKD	Mitral valve prolapse
Marfan	AR, MR, Aortic dissection



## Classification of CHD

### A) Congenital Cyanotic HD (20%)

- Congenital cyanotic HD
- Congenital acyanotic HD
- Others

#### Causes (Individual lesions)

Pulmonary Blood Flow	Pulmonary Blood Flow
<b>A) RVH</b> <ul style="list-style-type: none"> <li>▪ Fallot tetralogy</li> <li>▪ TGA with PS</li> <li>▪ DORV with PS</li> <li>▪ PS with VSD</li> <li>▪ Pulmonary atresia with VSD</li> </ul>	<b>A) RVH</b> <ul style="list-style-type: none"> <li>▪ TGA</li> <li>▪ TAPVR</li> <li>▪ HLHS</li> </ul>
<b>B) LVH</b> <ul style="list-style-type: none"> <li>▪ Tricuspid atresia</li> <li>▪ Pulmonary atresia</li> </ul>	<b>B) LVH, RVH or both</b> <ul style="list-style-type: none"> <li>▪ Single ventricle</li> <li>▪ Truncus arteriosus</li> </ul>
<b>C) RA Enlargement</b> <ul style="list-style-type: none"> <li>▪ Ebstein anomaly</li> </ul>	<b>C) Eisenmenger syndrome</b>

### Onset of Cyanosis

Early onset	Delayed onset (1-2m)	Variable onset
<ul style="list-style-type: none"> <li>▪ TGA</li> <li>▪ TAPVR</li> <li>▪ HLHS</li> <li>▪ Tricuspid atresia</li> <li>▪ Pulmonary atresia</li> </ul>	<ul style="list-style-type: none"> <li>▪ Fallot tetralogy</li> <li>▪ TGA with PS</li> <li>▪ DORV with PS</li> <li>▪ PS with VSD</li> <li>▪ Pulmonary atresia with VSD</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ebstein anomaly</li> <li>▪ Single ventricle</li> <li>▪ Truncus arteriosus</li> </ul>

### Features

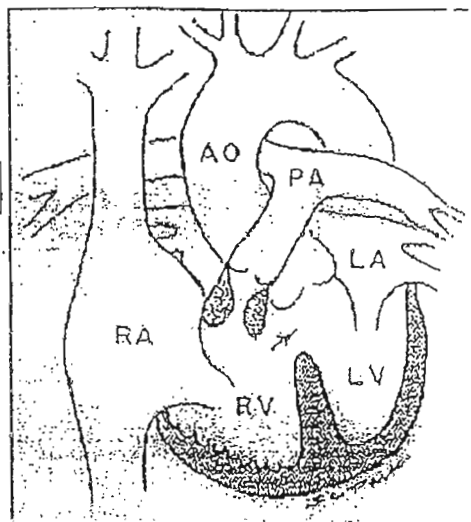
	Pulmonary Blood Flow	Pulmonary Blood Flow
<b>A) History</b> <ul style="list-style-type: none"> <li>▪ Recurrent chest infection</li> <li>▪ Squatting</li> <li>▪ HF</li> </ul>		
<b>B) Examination</b> <ul style="list-style-type: none"> <li>▪ Precordium</li> <li>▪ S<sub>2</sub></li> <li>▪ HF</li> </ul>		
<b>C) Investigation</b> <ul style="list-style-type: none"> <li>▪ CXR</li> <li>▪ ECG</li> <li>▪ ECHO</li> </ul>		

## Fallot Tetralogy

### Anatomical Defect

1. Infundibular PS
2. Big VSD
3. Overriding aorta
4. Mild RVH

Anterior deviation of the septum



### Hemodynamics

- ☑ Blood in the RV pass through 2 pathways:
  - Small part: Pulmonary artery (PS)
  - Large part: Aorta (Overriding) → Cyanosis
- ☑ Development of MAPCAs

### Clinical Picture

- Cyanosis (Early, delayed or absent!!)
- Clubbing
- Dyspnea
- Squatting. Why?
- No recurrent chest infection except...
- Hypercyanotic spells
- HF: Rare. When?
- Cardiac examination
  - No or Mild RVH
  - Harsh ejection systolic murmur at ULNB
  - Thrill (ULNB)
  - Single S2

Pink Fallot = Mild RV outflow #

### Hypercyanotic spell

#### Precipitating factors:

- Hypoxia
- Acidosis
- Infection
- Dehydration

#### C/P:

- Deepening of cyanosis
- RD
- Syncope, Coma & Convulsions
- Murmur (Disappears or ↓↓)

#### Management:

- O<sub>2</sub> therapy
- Positioning
- IV fluid
- NaHCO<sub>3</sub> (1-2 mEq/Kg, IV)
- Sedation (Morphine = 0.1 mg/Kg/dose, SC)
- β-Adrenergic blockers (Propranolol = 0.1 mg/Kg/dose, IV)

*Ketamine* *Propranolol*

#### Long-term management (Prevention):

- Avoid Precipitating factors
- β-Adrenergic blockers (Propranolol = 1 mg/Kg/dose, PO)
- Iron therapy
- Palliative or Definitive Rx



## Investigations

### ✗ CXR

- Heart: Coeur en Sabot
- Chest: Lung oligemia
- Large part: Aorta (Overriding) → Cyanosis

### ✗ ECG: Rt axis deviation & RVH

### ✗ ECHO

### ✗ Catheterization: Pressure, O<sub>2</sub> %, abnormal tract, angiography

### ✗ CBC: ↑↑ Hb & ↑↑ Hct

## Complications

1. Thrombosis
2. Brain abscess
3. Infective endocarditis
4. HF

## Treatment

### A) Medical

- Hypercyanotic spells
- Prostaglandin E<sub>1</sub> (0.05-0.2 µg/Kg/min), Why?
- Propranolol
- Infective endocarditis (Prophylaxis & Rx)
- Iron
- Exchange transfusion (FFP or albumin), When?

### B) Surgical

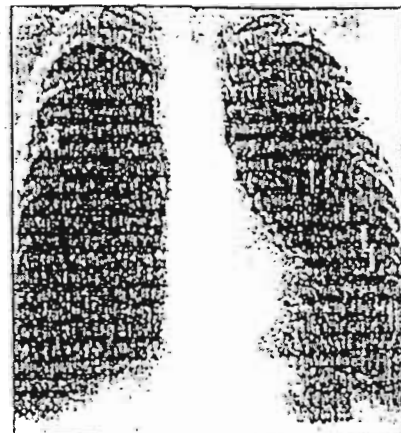
- Palliative: Blalock-Taussig (SCA + ipsilateral PA)

#### Indications:

- Hypoplastic PAs
- Weight < 2.5 Kg
- Age < 3 months
- b. Total correction (at 6-9 months)
  - Closure of VSD
  - Repair of RVOT

#### Complications:

- RY failure
- Pulmonary incompetence
- RBBB or HB



#### Hemiplegia in Fallot:

- Thrombosis
- Brain abscess
- Infective endocarditis

#### Side effects of PGE:

- Apnea
- Bradycardia
- Hypotension

#### Blalock-Taussig shunt (BT):

- Subclavian artery
- Ipsilateral PA

#### Other types shunt:

- Waterston
- Potts

## Transposition of the Great Arteries (TGA)

### Anatomical Defect

1. Aorta arises from RV
2. Pulmonary artery arises from LV
3. Communication is a must

### Hemodynamics

- ☑ 2 parallel circulations
  - LV → Pulmonary artery → ↑↑ PBF → LV
  - RV → Aorta (Cyanosis) → Body → RV
- ☑ ASD, VSD or PDA

3 Levels

### Clinical Picture

#### A) History

- Cyanosis (Early)
  - Onset: Within the 1<sup>st</sup> few hours or days of life
  - Not relieved by 100% O<sub>2</sub>
- Dyspnea
- Manifestations of HF (3 T)
- Recurrent chest infection (Cough...)

#### B) Examination

- a. General
  - FTT
  - Central cyanosis
  - Clubbing (1-2 yrs)
- b. Cardiac
  - Inspection & Palpation: Left parasternal pulsation (RVH)
  - Auscultation
    - Accentuated S2
    - Usually No murmur (Systolic murmurs may be present)

### Complications

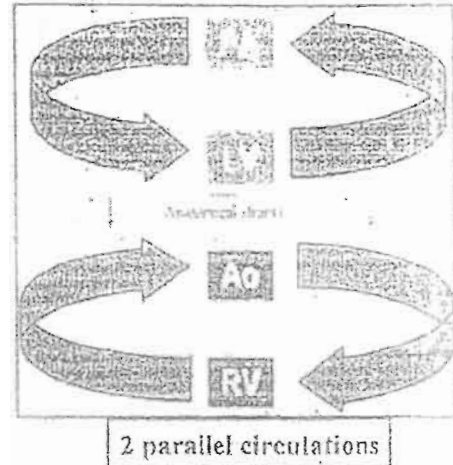
1. Thrombosis (Polycythemia)
2. Brain abscess (Loss of lung filter)
3. Infective endocarditis
4. HF & recurrent chest infection

### Investigations

- ☑ CBC: ↑↑ Hb & ↑↑ Hct
- ☑ CXR
  - Heart: Egg-on-side
  - Chest: Lung plethora (↑↑ PVMs)
- ☑ ECG: Hypertrophy of the RV
- ☑ ECHO
- ☑ Catheterization

### Treatment

- A) Balloon atrial septostomy: Rashkind procedure
- B) Total correction (at 2 wks): Arterial switch



- Cardiomegaly
- Egg-on-side
- Narrow pedicle

Arterial switch



## Management of CHD

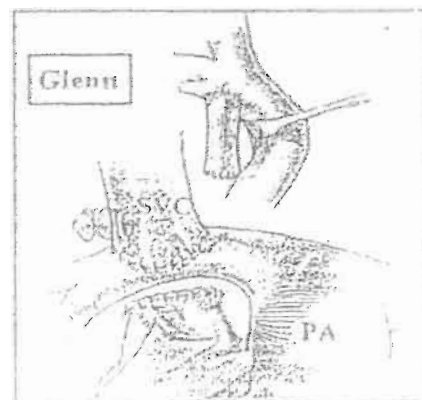
### Medical Management of CHD

1. Activity: Usually no restriction.
2. Diet: Well-balanced diet "Heart-healthy"
3. Vaccination: Routine + **Influenza**
4. Infective endocarditis (Prophylaxis & Rx)
5. Rx of HF & arrhythmias if present
6. Iron (↑↑ Exercise tolerance, ↑↑ RBC deformability & ↓↓ Stroke)
7. Hypercyanotic spells
8. Prostaglandin E1 (0.05-0.2 µg/Kg/min), When?
9. Propranolol in patients with infundibular stenosis (TOF)
10. Exchange transfusion (FFP or albumin), When?

Most patients who have mild CHD require no Rx

### Surgical (Interventional) Management of CHD

- a. Shunt operation (BT shunt)  
Anastomosis between subclavian artery & ipsilateral PA
- b. Repair of coarctation  
Resection + end-to-end anastomosis  
Subclavian flap aortoplasty
- c. Pulmonary artery banding  
- Palliative procedure to protect lung vascularity
- d. Arterial Switch  
- Performed for TGA before the age of 2 wks  
- Cutting aorta & pulmonary arteries & changing them around
- e. Glenn  
- Anastomosis between SVC & Rt PA →
- f. Fontan  
- Anastomosis between SVC & IVC to the Rt PA
- g. Norwood  
- Anastomosis between PA & ascending aorta →  
- Rt BT shunt  
- Atrial septostomy
- h. Rastelli  
Performed for TGA with VSD & PS  
- Cutting PA & connected it to the RV  
- Intracardiac tunnel between LV & aorta
- i. Rashkind (Balloon Atrial Septostomy)  
- ECHO-guided (Bedside)  
- Indicated in TGA, pulmonary atresia with intact septum  
- Improves mixing at the atrial level  
- Access: Umbilical vein or femoral vein (> 3 days)  
- Catheter is passed into RA then to the LA (across foramen ovale)  
- Inflation of the balloon at the end with rapid withdrawal → tear



## Complications of CHD

### A) Cardiac Complications

1. Infective endocarditis
2. HF
3. Arrhythmias

### B) Extra-cardiac Complications of cyanotic CHD

	Complication	Etiology	Therapy
1	Polycythemia	Hypoxia	Phlebotomy
2	Anemia	Nutritional (Iron;)	Iron
3	DIC	Polycythemia	Phlebotomy
4	Bleeding	DIC	Supportive
5	CNS abscess	Rt-Lt shunt (Loss of lung filter)	Antibiotics ± drainage
6	CNS stroke	Hge or thrombosis	Phlebotomy
6	Gum disease	Infection, bleeding, polycythemia	Dental hygiene
8	Gout	Polycythemia	Allopurinol
9	FTT	Nutritional, infection, hypoxia	↑↑ Calories, Rx of HF
10	Infection	Asplenia, DiGeorge	Antibiotics, Ribavirin
11	Pregnancy complications	Placental insufficiency, ↓↓ CO	Rest + Counseling
12	Psychological	Hospitalization, Cosmetic, ↓↓ activity	Counseling
13	Clubbing	Hypoxia	None
14	Arthritis	Hypoxia, Gout	None

### C) Post-operative Complications

1. CNS:
  - Coma
  - Convulsions
  - Focal lesions
  - Phrenic nerve injury
  - Horner syndrome
  - Pain & anxiety
2. Respiratory
  - Phrenic nerve injury
  - Vocal cord injury & Stridor
  - ARDS
  - Pulmonary edema
  - Pleural effusion
  - Chylothorax
  - Atelectasis
  - Pneumonia
3. CVS
  - Arrhythmias
  - HF & Cardiogenic shock
  - Pericardial effusion & tamponade
  - Post-pericardiotomy syndrome
4. Renal
  - Prerenal ARF (Hypovolemia)
  - Intrinsic ARF (ATN, prolonged prerenal...)
5. Metabolic
  - ↓↓ Na, ↓↓ Glucose, ↑↑ Glucose
  - Renal biopsy: (WHO grades SLE)
6. Blood
  - Bleeding (↓↓ PLT, ↑↑ PT, ↑↑ PTT)
  - Shunt thrombosis
  - DIC
  - GVHD (DiGeorge syndrome)
7. Infections
  - Wound infection, UTI, Hepatitis
  - Infective endocarditis

## Cyanotic CHD

	Anatomical defect	C/P	Cardiac	Investigations	
Pulmonary atresia with VSD	Pulmonary Atresia RV → LV → Aorta Duct dependent	Early-onset cyanosis HF may occur, when?	No murmur Murmurs (PDA or MAPCAs) Single S2		Medical: PGE1 + Supportive Surgical: Palliative (BT shunt) or total correction
Pulmonary atresia with intact ventricular septum	Pulmonary Atresia Hypoplastic RV (ASD) Duct dependent	Early-onset cyanosis RD No HF	No murmur Murmurs (PDA or MAPCAs) Single S2		Medical: PGE1 + Supportive Surgical: Palliative (BT shunt) or total correction or Fontan
Tricuspid atresia	Tricuspid Atresia (ASD) RA → LA → LV ± Duct dependent	Early-onset cyanosis HF may occur	Parastolic murmur (VSD) Single S2	Lt axis deviation ↑↑ P4-a	Medical: PGE1 + Supportive + B/ Surgical: Palliative (BT shunt) or Glenn or Fontan
DORV with PS	RV → Both Aorta & PA LV → VSD (only exit) PS	Fallot	Fallot		Medical: PGE1 + Supportive Surgical: Palliative (BT shunt) or total correction
DORV without PS	RV → Both Aorta & PA LV → VSD (only exit) No PS	Mild or No cyanosis HF	↑↑ S2		Medical: Supportive Surgical: Total correction
TGA	2 parallel circulations Blue blood in the body Pink blood in the lungs ASD, VSD or PDA (Mixture of blood)	Early-onset cyanosis Differential cyanosis (UL > LL) RD, FTT, clubbing HF may occur, when?	RVH Usually No murmur ↑↑ S2 (& Single)	Egg-on-side Narrow pedicle ↑↑ PVMs	Medical: PGE1 Surgical: BAS (Rashkind) or arterial switch (1 <sup>st</sup> 2 wks)
TGA with IVS	2 parallel circulations Intact ventricular septum	Early-onset cyanosis RD No HF	No murmur Single S2		Medical: PGE1 Surgical: BAS (Rashkind) or arterial switch (1 <sup>st</sup> 2 wks)
TGA with PS	2 parallel circulations Aorta is anterior & RT	Fallot	Fallot		Medical: PGE1 Surgical: BAS (Rashkind) or Rastelli
L-TGA (Corrected TGA)	TGA + Ventricular inversion			For the Associated anomalies	
Truncus arteriosus (TA)	Single trunk → Aorta & PA	If PS → Fallot-like No PS → TGA + VSD علاوة عكسية			
Single Ventricle	Single ventricle				

	Anatomical defect	C/P	Cardiac ex.	Investigations	Rx
Ebstein anomaly	Downward displacement of the tricuspid valve Huge RA + Small RV Rt-to-Lt shunt (PFO)	Variable-onset cyanosis ? Asymptomatic Arrhythmias (SVT)	Murmurs (TR)	RA enlargement WPW ↓↓ PVMs	Medical: PGEI + Supportive + Anti-arrhythmic drugs Surgical: Rarely needed
Hypoplastic Left Heart Syndrome (Death in the 1 <sup>st</sup> month)	Variable degrees of: Hypoplastic LA & LV Stenosis of Mitral & aortic Hypoplastic ascending aorta So, Duct dependent	Early-onset cyanosis Differential cyanosis (LL > UL) ↓↓ CO (Collapse) Absent pulses	RVH Usually No murmur ↑↑ S2 (& Single)	↑↑ PVMs RVH	Medical: PGEI + Supportive Surgical: Norwood
Total anomalous pulmonary VR (TAPVR)	All pulmonary veins are Not connected to the LA ▪ Supracardiac* ▪ Cardiac (3) ▪ Infracardiac ممكن Obstruction → Pulm** لازم ASD Duct dependent	Obstructed TAPVR Early-onset cyanosis RD No HF Non-obstructed No or mild cyanosis HF	Obstructed: No murmur Non-obstructed: Systolic murmurs ↑↑ S2 (& Single)	RVH Snowman Ct, MRI	Medical: PGEI + Supportive Surgical: BAS (Rashkind) or total correction NB: PGEI & BAS (Rashkind) are Not effective in obstructed TAPVR
Eisenmenger \$  Not common, why?	Pulmonary vascular disease as a complication of Lt to Rt shunt (VSD, ASD, PDA) with bidirectional or reversed shunt Hyperkinetic Pulm** then obstructive Pulm**	2 <sup>nd</sup> or 3 <sup>rd</sup> decades ممكن earlier (Down) Cyanosis RVF may occur	RVH Pulm**	Polycythemia ↑↑ PA	Prevention... Rx of complication of CHD Heart-Lung transplantation

## B) Congenital Acyanotic HD (80%)

### Causes (Individual lesions)

Pulmonary Blood Flow	Normal Pulmonary Blood Flow
A) RVH ▪ ASD (Östium secundum & primum) ▪ PAPVR	A) RVH ▪ PS
B) LVH ▪ PDA ▪ Aorticopulmonary defect (DD: TA)	B) LVH ▪ AS ▪ Coractation
C) RVH & LVH ▪ VSD ▪ ECD	

Isolated PFO:  
▪ No Lt-to-Rt shunt  
▪ No hemodynamic changes

### C) Others

#### 1 Anomalies of the aortic arch

##### 1. Right aortic arch

Description: Aorta curves to the Rt of the trachea

C/P:

- Isolated: Asymptomatic
- Associated with other CHD

Investigation:

- CXR: Trachea is shifted to the Lt
- Barium swallow: Indentation of the esophagus on its Rt side

##### 2. Vascular Rings

Definition: Congenital anomalies of the aortic arch & its major branches forming vascular rings & variable degrees of mechanical compression

	Description	C/P
Double aortic arch*	2 aortic arches completely encircle the trachea & esophagus	Respiratory + GIT
Rt aortic arch with Lt ligamentum arteriosum	2 completely encircle the trachea & esophagus	Respiratory + GIT
Anomalous innominate artery	Innominate artery arises too far to the Lt (or more posterior) → # Trachea	Respiratory
Aberrant Rt Subclavian artery	Rt SCA arises from the descending aorta → Passes behind the esophagus	GIT
Anomalous Lt PA Vascular sling	Lt PA arises from Rt PA → Passes between trachea & esophagus	Respiratory

C/P:

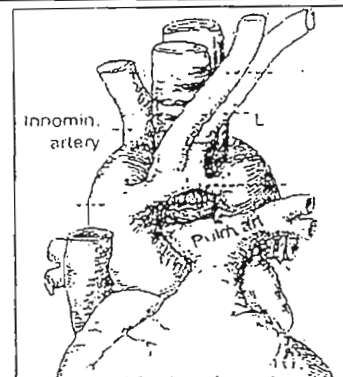
- Respiratory: RD, stridor, wheezes
- GIT: Swallowing, dysphagia
- Cardiac: May be present!!

Investigation:

- CXR & Barium swallow
- ECHO, CT, MRI, MRA

Rx:

Medical (Mild cases), Surgical (Severe cases)



## II Anomalies of the Coronary arteries

### 1. Coronary AV fistula

Anatomical defect: Fistula between a coronary artery & an atrium or ventricle

C/P: Similar to PDA...

Investigations: ECHO & Catheterization (Angiography)

Rx: Catheter or Surgical closure

### 2. Ruptured sinus of Valsalva aneurysm

Anatomical defect:

- Congenital weakness of the wall of one of the sinuses
- Rupture into an atrium or ventricle

C/P: Similar to PDA...

Investigations: ECHO & Catheterization (Angiography)

Rx: Surgical closure

### 3. Anomalous origin of Lt coronary artery from PA

Anatomical defect:

- Lt coronary artery arises from the PA (Not the aorta)
- LV is supplied by less oxygenated blood with less perfusion pressure
- Myocardial ischemia, infarction & fibrosis
- Anastomosis between Rt & Lt coronary arteries may develop
- Steal-phenomenon

If untreated, death  
in the 1<sup>st</sup> 6 months

C/P:

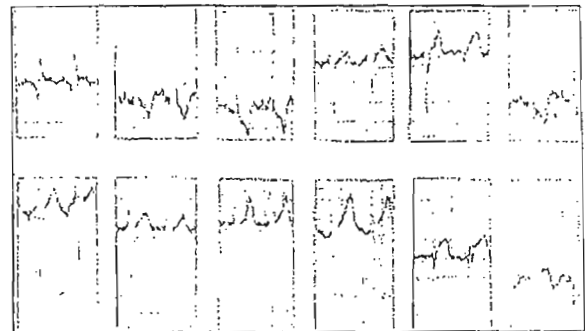
- Angina (Chest pain)
- HF & Cardiomegaly

Investigations:

- ECG: Q-waves
- CXR, ECHO & Catheterization (Angiography)

Rx:

- Medical: HF, Angina...
- Surgical repair



### 4. Anomalous origin of Rt coronary artery from PA

Anatomical defect:

- Rt coronary artery arises from the PA (Not the aorta)
- Anastomosis between Rt & Lt coronary arteries may develop
- ↓↓ Blood supply to the LV

C/P: Angina, HF & sudden death (in adolescence)

Investigations & Rx:

### 5. Ectopic origin with Aberrant proximal course of coronary artery

Anatomical defect:

- Coronary artery arises from the aorta (but ectopic)
- Course: between aorta & PA → ↓↓ Blood supply to the LV

C/P: Angina, HF & sudden death (in adolescence)

Investigations & Rx:

### III Anomalies of the Heart Position

#### 1. Ectopia cordis

- Heart is displaced outside the chest through
  - a. Sternal defect
  - b. Diaphragmatic defect
- Poor prognosis: Infection, HF (associated CHD)

#### 2. Diverticulum of the LV

- Diverticulum protruding from the LV into the epigastrium
- Rx: Surgical repair

#### 3. Dextrocardia

Dextrocardia: Heart to the right, it may be:

- Isolated: (↑↑ risk of CHD)
- Part of situs inversus totalis: (No ↑↑ risk...)

Approach to diagnosis of heart position:

##### a. Visceroatrial situs

- Done by CXR, Abominal US & ECHO
  - Situs solitus
    - RA is on the RT, LA is on the LT
    - Liver is on the Rt, Stomach & spleen are on the LT
    - Three-lobed lung is on the Rt, Bi-lobed lung is on the Lt
  - Situs inversus (*The opposite...*)
  - Situs indeterminus (Heterotaxia): can be classified into:
    1. Asplenia (= Rt isomerism, Bilateral Rt-sidedness)
    2. Polysplenia (= Lt isomerism, Bilateral Lt-sidedness)

	Asplenia	Polysplenia
Spleen	Absent	Multiple
Lungs	Both lungs are trilobed	Both lungs are Bilobed
Stomach	Rt-sided	Lt-sided
Liver	Midline	Absence of the intrahepatic IVC
GB	Present	Absent
Malrotation (small intestine)	More common	Less common
Risk of sepsis	Yes	No
Mortality	High	Less
TAPVR	70-80%	Rare
TGA	70%	15%
IVC	Normal	Absent IVC with azygous continuation

##### b. Localization of the ventricles

- Done by ECHO
- Embryonic cardiac loop (d-loop): Normal A-V concordance
- Embryonic cardiac loop (L-loop): RA → LV  
LA → RV

Ventricular inversion

##### c. Localization of the great vessels

- Done by ECHO
- Normal or TGA

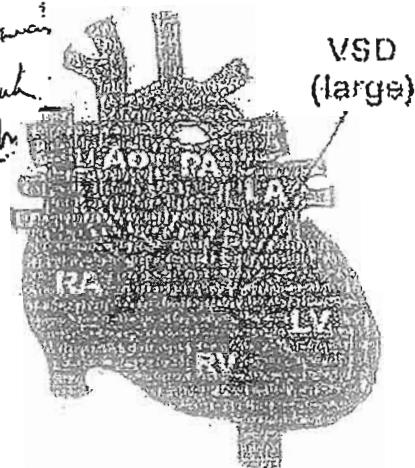
## Ventricular Septal Defect

(VSD)

### Anatomical Defect

1. Defect in the interventricular septum:
  - Site: Membranous (More common) or Muscular
  - Number: Single or multiple
2. VSD may be isolated or associated with other CHD (25%)

→ Membran  
→ Muscular  
→ Subaortic  
→ Conduction system



### Hemodynamics

- ☒ Blood is shunted from the LV to RV during the systole
- ☒ No shunt occurs during diastole
- ☒ ↑↑ PBF (Lung plethora)
- ☒ Biventricular hypertrophy

### C/P of Small VSD

A) History: Asymptomatic

B) Examination

- a. General: Normal
- b. Cardiac
  - Inspection & Palpation: Systolic thrill over the Lt parasternal area
  - Auscultation: Murmur...
- c. Investigations:
  - CXR, ECG: Normal
  - ECHO: Diagnostic
- d. Treatment
  - Reassurance (Spontaneous closure is common specially in muscular VSD)
  - Infective endocarditis (Prophylaxis & Rx)

### C/P of Large VSD

A) History

- Feeding difficulties & FTT
- Dyspnea, exercise intolerance
- Manifestations of HF (3 T)
- Recurrent chest infection (Cough...)

B) Examination

- a. General
  - FTT
  - Recurrent chest infection
- b. Cardiac
  - Inspection & Palpation
    - Biventricular hypertrophy
    - Systolic thrill over the Lt parasternal area
  - Auscultation
    - Accentuated S2 (Pulmonary component)
    - Murmur
      - Timing: Pansystolic
      - Character: Harsh
      - Maximum intensity: Lt parasternal area (3<sup>rd</sup> & 4<sup>th</sup> spaces)
      - Selective propagation: All over the precordium

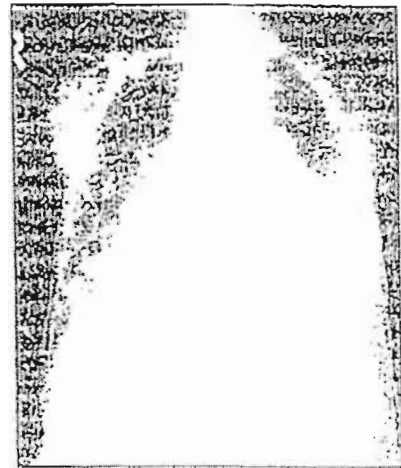


## Complications

1. HF
2. Recurrent chest infections
3. Infective endocarditis
4. Eisenmenger syndrome: Reversal of the shunt across the VSD due to pulmonary hypertension with appearance of cyanosis in previously acyanotic child

## Investigations

- ☒ CXR
  - Heart: Biventricular enlargement ➡
  - Chest: Lung plethora (↑↑ PVMs)
- ☒ ECG: Biventricular hypertrophy
- ☒ ECHO
- ☒ Catheterization



## Treatment

### A) Medical

- Infective endocarditis (Prophylaxis & Rx)
- Proper nutrition
- Management of HF (Preload, afterload, inotropes), How?

### B) Surgical

- Closure (In stable child with moderate VSD, delay surgery? spontaneous closure)

## Atrial Septal Defect (ASD)

### Anatomical Defect

Defect in the interatrial septum:

1. Ostium secundum	2. Ostium primum
More common	Less common
Less serious	More serious
High defect	Defect in the lower IAS
Normal mitral valve	Cleft anterior leaflet
No mitral regurge	Mitral regurge



### Hemodynamics

- ☒ Blood is shunted from the LA to RA during the systole
- ☒ ↑↑ PBF (Lung plethora)
- ☒ Rt ventricular hypertrophy

		Ostium secundum	Ostium primum
History	Onset	Usually in the 3 <sup>rd</sup> or 4 <sup>th</sup> decades	Infancy
	Symptoms	<ul style="list-style-type: none"> <li>• Asymptomatic</li> <li>• Dyspnea, exercise intolerance</li> <li>• Recurrent chest infection</li> <li>• HF</li> </ul>	<ul style="list-style-type: none"> <li>• Dyspnea, exercise intolerance</li> <li>• Recurrent chest infection</li> <li>• HF</li> </ul>
Examination	Insp. & Palp.	RVH	Biventricular enlargement
	S2	Wide fixed splitting	
	Murmur	No murmur due to ASD	
		Ejection Systolic over pulmonary area due to relative PS	
Investig.			Murmur of MR (Why?)
	<ul style="list-style-type: none"> <li>▪ CXR</li> <li>▪ ECG</li> <li>▪ ECHO</li> <li>▪ Catheter.</li> </ul>	RVH	Biventricular enlargement  (Catheterization may be needed)
Rx		Catheter coil closure	Surgery

## Patent Ductus Arteriosus (PDA)

### Incidence & Etiology

Congenital Rubella syndrome, Prematurity, ♀ > ♂

### Anatomical Defect

1. Persistence of the ductus arteriosus
2. Site: Just distal to the origin of the Lt Subclavian artery

### Hemodynamics

- ☒ Blood is shunted from Aorta to PA during systole & diastole
- ☒ ↑↑ PBF (Lung plethora)
- ☒ Lt ventricular hypertrophy

### C/P of Small PDA As small VSD

A) History: Asymptomatic

B) Examination

- a. General: Normal
- b. Cardiac: Murmur...
- c. Investigations:
- d. Treatment
  - Ligation
  - Infective endocarditis (Prophylaxis & Rx)

### C/P of Large PDA

A) History: As large VSD

B) Examination

- a. General
  - FTT
  - Recurrent chest infection
  - Hyperdynamic circulation ⇨
- b. Cardiac
  - Inspection & Palpation
    - Lt ventricular hypertrophy
    - Systolic thrill over the Lt infraclavicular area
  - Auscultation
    - Accentuated S<sub>2</sub> (Pulmonary component)
    - Murmur
      - Timing: Continuous
      - Character: Machinery
      - Maximum intensity: Lt infraclavicular area
      - Selective propagation: Pulmonary area (Lt 2<sup>nd</sup> intercostal space)

### Complications As VSD (4)

### Investigations

- ☒ CXR
  - Heart: LV enlargement
  - Chest: Lung plethora (↑↑ PVMs)
- ☒ ECG (LV hypertrophy), ECHO, Catheterization

### Treatment As VSD (Catheter closure can be done)



**Function of the ductus**  
Shunting of blood from PA to Aorta  
**Closure of the ductus**

- Functional: Soon after birth (O<sub>2</sub>)
- Structural: Within weeks

**Hyperdynamic Circulation:**

- Big pulse volume
- Water-hammer pulse
- HR: Tachycardia
- BP: Big pulse pressure?
- Prominent carotid pulses

## Coarctation of Aorta

### Anatomical Defect

1. Localized narrowing of the aorta
2. Site: Any point from the arch down to the iliac bifurcation
3. Commonest site: Just distal to the origin of the Lt SCA

### Hemodynamics

- ☑ Pressure gradient across the aorta
- ☑ ↑↑ BP in the upper part of the body
- ☑ ↓↓ BP in the lower part of the body
- ☑ Lt ventricular hypertrophy
- ☑ Development of collaterals (Subclavian, descending aorta & Femoral)



### Presentations

1. Accidentally: Murmur
2. Femoral pulses: Not felt
3. Hypertension: Unexplained
4. Complications: Intracranial Hge, Infective endocarditis

### Clinical Picture

A) History: Usually asymptomatic (4 clinical situations)

B) Examination

a. General:

- Weak or absent femoral pulses or radio-femoral delay.
- Hypertension

b. Cardiac

- Inspection & Palpation
  - Lt ventricular hypertrophy
- Auscultation
  - Murmur
    - Timing: Systolic
    - Character: Harsh
    - Maximum intensity: Inter-scapular area
    - Selective propagation: Anterior chest wall

#### Causes of Hypertension:

- Mechanical
- ↓↓ Renal perfusion

### Complications

1. HF
2. Intracranial Hge (Subarachnoid)
3. Infective endocarditis

### Investigations

- ☑ CXR
  - Heart: LV enlargement
  - Chest: Rib notching (Older children)
- ☑ ECG (LV hypertrophy); ECHO, Catheterization

### Treatment

A) Medical (Infective endocarditis & HF)

B) Surgical

- Coarctectomy (Resection-anastomosis).
- Balloon angioplasty can be used if restenosis (Recurrence)

## Aortic Stenosis

## Pulmonary Stenosis

	Aortic Stenosis	Pulmonary Stenosis
Anatomical Defect	Congenital aortic stenosis: <ul style="list-style-type: none"> <li>▫ Valvular (Fusion of the cusps)</li> <li>▫ Supravalvular (in William syndrome)</li> <li>▫ Subvalvular</li> </ul>	Congenital pulmonary stenosis
Hemodynamics	<input checked="" type="checkbox"/> Obstruction of blood flow from LV <input checked="" type="checkbox"/> Pressure gradient across aortic valve <input checked="" type="checkbox"/> Lt ventricular hypertrophy	<input checked="" type="checkbox"/> Obstruction of blood flow from RV <input checked="" type="checkbox"/> Pressure gradient across Pulm. valve <input checked="" type="checkbox"/> Rt ventricular hypertrophy
Clinical Picture	A) History <ul style="list-style-type: none"> <li>- Asymptomatic</li> <li>- Low CO symptoms: Anginal pain, Fatigue, Syncope (in severe cases)</li> <li>- Manifestations of Lt sided HF</li> </ul> B) Examination <ul style="list-style-type: none"> <li>a. General               <ul style="list-style-type: none"> <li>▫ Pulse: Small volume (Plateau)</li> <li>▫ BP: ↓↓ Systolic BP</li> </ul> </li> <li>b. Cardiac               <ul style="list-style-type: none"> <li>▫ Inspection &amp; Palpation:                   <ul style="list-style-type: none"> <li>- LV hypertrophy</li> <li>- Systolic thrill (2<sup>nd</sup> Rt space)</li> </ul> </li> <li>▫ Auscultation                   <ul style="list-style-type: none"> <li>- ↓↓ S2 (± Paradoxical splitting)</li> <li>- Murmur</li> <li>Harsh ejection systolic</li> <li>Max. intensity: 2<sup>nd</sup> Rt space</li> <li>Selective propagation: Carotids</li> <li>Apex</li> </ul> </li> </ul> </li> </ul>	A) History <ul style="list-style-type: none"> <li>- Asymptomatic</li> <li>- Low CO symptoms: Anginal pain, Fatigue, Syncope (in severe cases)</li> <li>- Manifestations of Rt sided HF</li> </ul> B) Examination <ul style="list-style-type: none"> <li>a. Cardiac               <ul style="list-style-type: none"> <li>▫ Inspection &amp; Palpation:                   <ul style="list-style-type: none"> <li>- RV hypertrophy</li> <li>- Systolic thrill (2<sup>nd</sup> Lt space)</li> </ul> </li> <li>▫ Auscultation                   <ul style="list-style-type: none"> <li>- ↓↓ S2 (± Wide splitting)</li> <li>- Murmur</li> <li>Harsh ejection systolic</li> <li>Max. intensity: 2<sup>nd</sup> Lt space</li> <li>Selective propagation: Infraclav.</li> </ul> </li> </ul> </li> </ul>
Complications	<ul style="list-style-type: none"> <li>▫ HF</li> <li>▫ Infective endocarditis</li> </ul>	<ul style="list-style-type: none"> <li>▫ HF</li> <li>▫ Infective endocarditis (Rare)</li> </ul>
Investigations	LV hypertrophy	RV hypertrophy
Treatment (When?)	<ul style="list-style-type: none"> <li>▫ Balloon valvuloplasty</li> <li>▫ Surgical valvotomy (thickened cusps)</li> <li>▫ Valve replacement (avoid till growth)</li> </ul>	<ul style="list-style-type: none"> <li>▫ Balloon valvuloplasty</li> <li>▫ Surgical valvotomy (thickened cusps)</li> </ul>

## Duct dependant circulation

These are circulations that depend on the ductus arteriosus to maintain pulmonary or systemic blood flow. Deterioration usually occurs when the duct close in the 1<sup>st</sup> week

### 1. Duct dependant pulmonary blood flow

- Tetralogy of Fallot
- Pulmonary atresia with VSD
- DORV with PS
- Pulmonary atresia with intact septum
- Tricuspid atresia
- Ebstein anomaly
- TGA
- Critical pulmonary stenosis

### 2. Duct dependant systemic blood flow)

- Hypoplastic left heart
- Interrupted aortic arch
- Coarctation of the aorta
- Critical aortic stenosis

Emergency neonatal treatment with prostaglandine E1 is life saving  
O<sub>2</sub> therapy should be...

## Rheumatic Fever

### Definition

It is an autoimmune inflammatory disease following upper respiratory tract infection with group A- $\beta$ -hemolytic streptococci involving the joints, heart, CNS, skin, SC tissue

5

### Incidence

- Age: Peak incidence = 5-15 yrs (All ages can be affected except young infants)
- Sex: Chorea is more common in ♀
- More common in developing countries

### Etiology

- It is an autoimmune following infection with of group A  $\beta$ -hemolytic streptococci
- Site of infection: throat (Pharyngitis)
- Latent period: 2-3 weeks (Several months in rheumatic chorea)

### Pathogenesis (Mechanism of tissue injury) →

- Autoimmune disease due to molecular mimicry between Streptococci & tissue antigens
- Antibodies formed against Streptococcal antigens react with human tissue antigens



### Pathology

- Proliferative lesions: Aschoff nodules
- Exudative lesion: Effusion

### Diagnosis [Modified Jones criteria]

Major Criteria	Minor Criteria	Evidence of recent Strept. Infection
Polyarthrititis	Fever	Recent scarlet fever
Carditis	Arthralgia	Antistreptolysin O titer (ASOT)
Chorea	Prolonged PR interval	Antistreptokinase
Erythema marginatum	Acute phase reactants:	Antihyaluronidase
SC nodules	▪ ESR	Throat culture
	▪ CRP	
	▪ Leucocytosis	

### Interpretation of Jones Criteria

- Diagnosis of rheumatic fever depend on:
  - Two major or One major & Two minor criteria AND
  - Evidence of recent streptococcal infection
- Diagnosis based on 2 major criteria is stronger than that based on 1 major & 2 minors
- Arthralgia should Not be considered as a minor criterion in patients with arthritis
- Fever  $> 39.5^{\circ}\text{C}$  is very unusual in rheumatic fever
- ESR, CRP & Leucocytosis are all considered as one minor criterion
- Exceptions of Jones criteria:
  - Chorea (Rheumatic chorea can be the only manifestation of rheumatic fever)
  - Late-onset carditis
  - Rheumatic recurrence in patients with documented RHD

3

What is the difference between Arthritis & Arthralgia?

- Pain
- Hotness, redness, swelling, limitation of movements

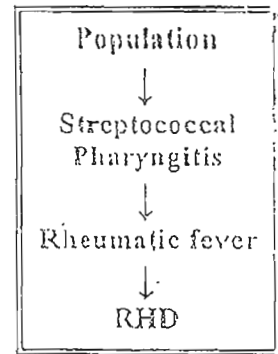
## Major Criteria

### A) Polyarthritis (75% of cases)

- Polyarticular (Never monoarticular)
- Large joints: Knees, ankles, wrists, elbows
- Arthritis: Redness, hotness, tenderness, swelling with limitation of movements
- Migratory (from joint to the other)
- Leaves the joint completely free
- Spontaneous resolution (even without Rx)
- Dramatic response to salicylates

### B) Carditis (50% of cases)

- It is the most serious
- May be late-onset (Delayed)
- It is Pancarditis
  - c. Pericarditis
    - Stitching chest pain
    - Pericardial rub
  - d. Myocarditis
    - Muffled heart sounds
    - Heart failure
    - Tachycardia (Disproportionate to the degree of fever)
  - e. Endocarditis
    - Lt sided valves > Rt sided valves
    - Mitral > Aortic
    - ☑ Acute stage
      - Carey-Coombs murmur: Mid-diastolic due MS (Edema of the cusps)
      - Mitral regurge: Damage of the cusps. (Describe MR murmur??)
    - ☑ Chronic stage (Fibrosis)
      - Stenosis
      - Incompetence (Regurgitation)
      - Double lesion



HR ↑↑ by 10-15/min for each  
1°C ↑↑ in body temperature

### C) Chorea (10% of cases)

- It is the most common cause of chorea in children (♀ > ♂)
- It the only neurological manifestation of rheumatic fever
- Rheumatic chorea can be the only manifestation of RF (Latent period = Months)
- Three main manifestations:
  - a. Chorea
    - Involuntary, static, irregular, sudden, jerky, semi-purposeful movements involving mainly the face, trunk & limbs, aggravated by emotional stress
  - b. Hypotonia
    - Darting tongue: The tongue can not be protruded for longer than few seconds
    - Milk-maid grip: Inability to maintain hand grip
    - Pendular knee reflex
    - Boat-shaped hands: hyperextension at the MCP & IP joints + flexion at the wrist
    - Pronator sign: The arm & palm turn out when held above the head
    - Arm extension: Wavy finger movement (Piano-player sign)
  - c. Emotional lability

Paralytic chorea (Chorea mollis):  
severe weakness & hypotonia



**D) Erythema marginatum:** (5% of cases)

- Site: Trunk & proximal parts of the limbs
- Shape: Erythematous nonpruritic macules [Sharp progressive margin & central fading]
- Recurrent & evanescent

**E) Subcutaneous nodules** (1% of cases)

- Site: Over bony prominences (Elbows, knees...)
- Shape: Painless, rounded, hard, small nodules (0.5-2 cm)
- Indicates severe carditis

**Investigations****A) Acute phase reactants**

- ☒ ESR
- ☒ CRP
- ☒ Leucocytosis

**B) Evidence of recent Streptococcal infection:**

- ☒ Antistreptolysin O titer (ASOT) > 300 Todd units
- ☒ Antistreptokinase
- ☒ Antihyaluronidase
- ☒ Throat culture

**Evidence of recent Strept. Infection:**

- Antistreptolysin O titer (ASOT)
- Antistreptokinase
- Antihyaluronidase
- Throat swab culture

**C) Cardiac assessment**

- ☒ CXR
- ☒ ECG
- ☒ Echocardiography

**Differential Diagnosis****1. Arthritis**

## • Infections

- Septic arthritis (Staph. \*...)
- Osteomyelitis (sympathetic effusion)
- Toxic synovitis of the hip joint
- Reactive arthritis

- Viral arthritis (EBV, CMV, HSV, VZV, HBV, Parvovirus B19)
- Tuberculous arthritis
- Lyme disease (Borrelia burgdorferi)

## • Collagen-vascular diseases

- SLE
- JRA
- Dermatomyositis

- Henoch-Schonlein purpura
- Kawasaki disease
- Familial Mediterranean Fever (FMF)

## • Hematological diseases

- Sickle cell anemia
- Leukemia

- Hemophilia

## • Malignancy

- Leukemia
- Lymphoma
- Neuroblastoma

## • Traumatic arthritis

## • Metabolic

**2. Carditis**

- CHD
- Myocarditis
- Innocent murmurs
- SLE

**3. Chorea**

- Other causes of chorea: Wilson
- Other movement disorders: Tics (Involuntary, irresistible, purposeless movements)

## Prevention

- Prevention of Streptococcal infection: Good housing & adequate ventilation
- Early diagnosis of Streptococcal infection
- Proper Rx of Streptococcal infection
  - Oral Penicillin V: for full 10 days (Even with early improvement of symptoms)
  - IM Benzathine penicillin: 600.000-1.200.000 IU (Sensitivity skin test is essential)
  - Oral erythromycin: in patients allergic to penicillin
- Prevention of recurrence of rheumatic fever
  - IM Benzathine penicillin: 1.200.000 IU every 3-4 wks (Sensitivity skin test...)
  - Duration: RF without carditis (5 yrs), RF with carditis (10 yrs), RHD (Life-long)

## Complications

A) Early: Heart failure, arrhythmias

B) Late: Rheumatic heart disease, rheumatic activity (Recurrence), Infective endocarditis

## Treatment

### A) Supportive Management

#### a. Diet:

- Salt restriction in cases of heart failure
- Fluid restriction in cases of heart failure

#### b. Rest: in patients with carditis & arthritis (Rheumatic activity)

### B) Specific Management

#### a. Arthritis or (Carditis without cardiomegaly):

- Salicylates 100 mg/Kg/day (tid) for 2 weeks
- 75 mg/Kg/day (tid) for 4-6 weeks

#### b. Carditis with Cardiomegaly or HF:

- Prednisone: 2 mg/Kg/day (tid) for 2-3 weeks with gradual tapering (Over 2 wks)
- Salicylates: 75 mg/Kg/day (tid) started with tapering & continued for 6 wks

#### c. Chorea:

- Phenobarbitone: 3-5 mg/Kg/day
- Haloperidol: 0.01-0.03 mg/Kg/day (in patients > 12 yrs)

### C) Rx of complications

#### a. Heart failure:

- Mild cases: Rest, Oxygen, fluid restriction, steroids
- Severe cases:
  - Preload reduction: Diuretics (Furosemide 1-2 mg/Kg/day)
  - Afterload reduction: ACE inhibitors (Captopril 0.5-1 mg/Kg/day)
  - Inotropes: Digitalis
    - Digitalizing dose: 0.04 mg/Kg
    - Maintenance dose: 0.01 mg/Kg/day

Digitalis should be given cautiously, why?

#### b. Rheumatic heart disease:

- Medical: HF, Infective endocarditis, rheumatic activity
- Surgical: Valve repair or replacement

NB: Diagnosis of RHD should include:


- Evidence of rheumatic nature
- Detection of chamber enlargement
- Detection of valve lesions
- Detection of complications

## Arrhythmias

### Definition

Abnormalities in heart rate, rhythm or relationship between atrial & ventricular contractions

### Physiology

- SAN is the **normal** pacemaker of the heart 
- SAN is controlled by both vagal & sympathetic nerves
- AVN is the **only** electrical connection between atria & ventricles
- AVN allows passage of impulses in **one** direction only (No retrograde conduction)
- AVN has long refractory period (↓↓ Conductivity, why?)
- AVN has maximum rate of AV conduction above which physiologic heart block occurs
- AVN is controlled by both vagal & sympathetic nerves
- Bundle of His → 2 bundle branches → Purkinje fibers
- Ventricles are supplied by sympathetic fibers but **not** the Vagus



Vagal Escape phenomenon

### Electrical Classification

#### 1. SAN

- Sinus tachycardia\*
- Sinus bradycardia
- Sinus arrhythmia
- Sick sinus syndrome (Brady)

#### 2. AVN

- Nodal premature beats
- Nodal rhythm
- Nodal tachycardia\*

#### 3. Atria

- Atrial flutter\*
- Atrial fibrillation\*
- Premature atrial contractions
- Atrial tachycardia\*
- Wandering pacemaker

#### 4. Ventricles

- Ventricular premature beats
- Ventricular tachycardia\*
- Ventricular fibrillation

#### 5. Heart block:

- 1<sup>st</sup> degree HB
- 2<sup>nd</sup> degree HB
- 3<sup>rd</sup> degree HB
- Bundle branch block

### Clinical Classification

#### 1. Tachyarrhythmias:

#### 2. Bradyarrhythmias:

3. Arrhythmias with normal HR: Sinus arrhythmia, extrasystoles, some forms of HB

### Etiology (May be idiopathic)

1. Myocarditis & cardiomyopathy
2. RHD (MS), CHD (Ebstein), surgery
3. Thyrotoxicosis
4. Electrolyte disturbances (↑↑ K), hypoxia & shock
5. Drugs: Digitalis & sympathomimetics (amphetamine)
6. Pre-excitation syndromes (WPW)

### Clinical Picture

- Asymptomatic
- Palpitation, ↓↓ CO manifestations & HF
- Sudden death may occur

### Investigations

- ECG & 24 hr-Holter monitoring
- EPS (Catheterization)

Age	Mean (Range)
Newborn	145 (90-180)
6 months	145 (90-180)
1 yr	132 (105-170)
2 yr	120 (90-150)
6 yr	100 (65-135)
10 yr	90 (65-130)

## Tachyarrhythmias

### Sinus Tachycardia

#### Definition

- SAN discharges at higher rate for age (usually  $<225/\text{min}$ )
- SAN is the pacemaker "Sinus rhythm"  $\Rightarrow$

#### Sinus rhythm:

- Each QRS is preceded by P wave
- P-wave is upright in lead II & inverted in aVR

#### Etiology

- Physiological: Anxiety, exercises, emotional stress, pain, crying
- Pathological: Fever, hypoxia, HF, shock, anemia, thyrotoxicosis, myocardial diseases

#### ECG

- Tachycardia
- Sinus rhythm...

#### Treatment

Rx of the cause

### Ventricular Tachycardia

#### Definition

- It is tachyarrhythmia originating from the ventricles
- A-V dissociation occurs as there is "No retrograde conduction"

#### Mechanism

Ventricular ectopic focus (120-240/min)

#### Etiology (May be idiopathic\*)

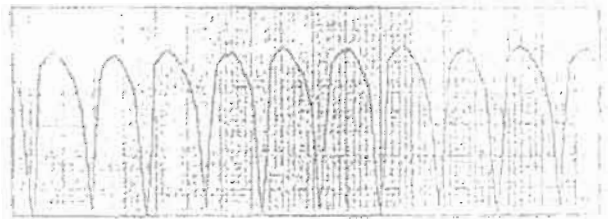
+ LQTS

#### Clinical Picture

- VT usually occurs in attacks (Sudden onset & termination)
- HR = 120-240/min
- Palpitation &  $\downarrow\downarrow$  CO manifestations
- Sudden death if VF occurs

#### ECG

- Regular tachycardia (120-240/min)
- Wide & bizarre QRS-complexes
- P-wave: usually masked (A-V dissociation)



#### Treatment (Rx of the cause)

##### A) Hemodynamically stable

- Lidocaine:
  - The drug of choice in PVCs & VT
  - Dose: IV bolus (1-2 mg/Kg) followed by continuous infusion of 30-50  $\mu\text{g}/\text{Kg}/\text{min}$
- Other drugs: Amiodarone, propranolol & procainamide

##### B) Hemodynamically unstable

- Synchronized DC shock [1-2 J/Kg], can be repeated

#### Prevention of Recurrence

- Propranolol in patients with LQTS
- Radiofrequency (or surgical) ablation
- Implantable cardioverter-defibrillator (ICD)

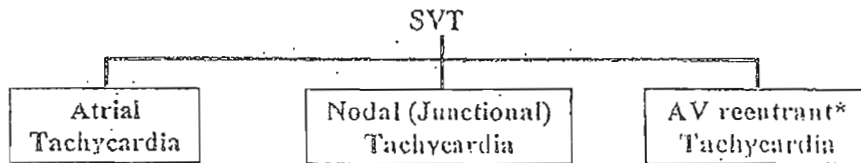


## Supraventricular Tachycardia

### Definition

- It is the most common tachyarrhythmia in children, originating in the atria or AVN

### Types



### Mechanism

A) **Reentrant:** Two pathways are involved; one of them is the AVN & the other is either:

- Accessory pathway e.g., bundle of Kent in Wolff-Parkinson-White preexcitation
- Functional bypass tract within the AVN "Dual AVN"

B) **Ectopic focus**

- Atrial tachycardia
- Nodal (Junctional) tachycardia

### Etiology (May be idiopathic\*)

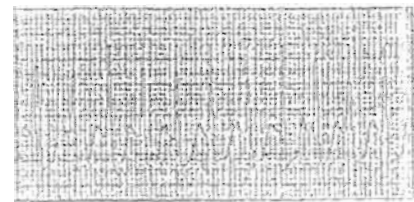
- |                                 |   |
|---------------------------------|---|
| 1. Myocarditis & cardiomyopathy | 4. Electrolyte disturbances (↑↑ K), hypoxia & shock |
| 2. RHD (MS), CHD (Ebstein)      | 5. Drugs: Digitalis & sympathomimetics              |
| 3. Thyrotoxicosis               | 6. Pre-excitation syndromes (WPW)                   |

### Clinical Picture

- Intrauterine SVT: Hydrops (Non-immune)
- SVT-usually occurs in attacks (Sudden onset & termination)
- HR = 180-300/min (Junctional tachycardia has relatively slower rate 120-200/min)
- Many infants tolerate SVT for up to 6-12 hr then **CHF** occurs (Hemodynamic instability)
- Palpitation & ↓↓ CO manifestations

### ECG

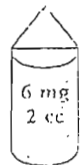
- Regular tachycardia (180-300/min)
- Narrow QRS-complex (may be wide!!)
- P-wave: Absent, abnormal or inverted (before or after QRS)



### Treatment

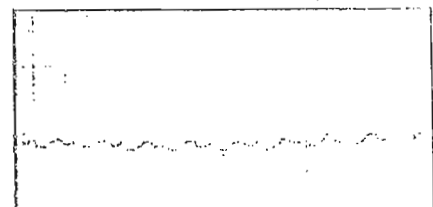
A) **Hemodynamically stable:** (Vagal stimulation & Drugs)

- Infants: Ice-water applied to the face or immersion of the face in ice-water (Diving reflex)
- Older children: Unilateral carotid sinus massage, ~~pressure on eyeball~~ or Valsalva
- Adenosine:
  - The drug of choice in SVT
  - Rapid IV injection followed by saline flush (CVL is preferred)
  - Dose: Start with 100 µg/Kg with increment of 50 µg/Kg every 1-2 min if no response
- Amiodarone: Used in atrial & junctional tachycardia
- Other drugs: Verapamil, procainamide



B) **Hemodynamically unstable**

- Synchronized DC shock [0.5-2 J/Kg], can be repeated



### Prevention of Recurrence

- Propranolol, Sotalol (12 months)
- Radiofrequency (or surgical) ablation of the accessory pathway in WPW syndrome
- Diagnosis of WPW syndrome: Digitalis is CI

## Atrial Flutter

### Definition

- It is tachyarrhythmia originating from an atria
- The atria discharge at a **regular** high rate (250-400/min)
- Due to physiologic HB, only 1/2, 1/3 or 1/4 of atrial impulses are transmitted to the ventricles

Mechanism Atrial ectopic focus (250-400/min)

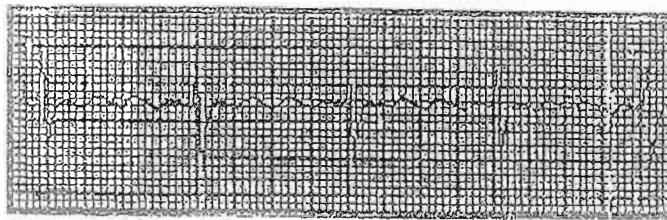
### Etiology

### Clinical Picture

- HR = 100-320/min
- Palpitation, ↓↓ CO manifestations & CHF

### ECG

- Flutter waves (F-waves)
- Saw-tooth appearance
- Regular atrial rhythm with a rate of 250-400
- Ventricular response of 2:1, 3:1, 4:1 or higher (multiple F-waves before each QRS)
- Narrow QRS-complex



### Treatment

#### A) Acute situation:

- Synchronized DC shock [0.5-2 J/Kg], can be repeated
- Amiodarone

#### B) Chronic atrial flutter

- Exclude intra-atrial thrombosis, how?
- Anticoagulation before & after cardioversion

#### C) Rate control

- Propranolol, verapamil, digitalis (*In the past, digoxin was popular for this purpose*)
- Amiodarone

## Atrial Fibrillation

### Definition

- It is tachyarrhythmia originating from the atria at an **irregular** high rate (350-700/min)
- Due to physiologic HB, ventricular rate is only 120-180/min

### Mechanism & Etiology

### Clinical Picture

- HR = 120-180/min
- Palpitation, ↓↓ CO manifestations & CHF
- Thromboembolic manifestations

### ECG

- No P waves in ECG (f-waves)
- Absence of isoelectric line
- Irregular atrial rhythm (rate = 350-400)
- Irregular ventricular rhythm (rate = 120-180)
- Narrow QRS-complex



### Treatment

A) Acute situation (Recent-onset AF): Synchronized DC shock [0.5-2 J/Kg]

B) Chronic AF

C) Rate control

## Extrasystoles (Premature Beats)

### Definition

Premature discharge of an ectopic focus which may be atrial, junctional or ventricular

### Etiology

- Physiological: Anxiety, emotional stress, pain, crying
- Pathological: Fever, hypoxia, HF, shock, thyrotoxicosis, myocardial diseases, drugs...

### Clinical Picture

- Palpitation (Extra, missed or heavy beats)
- Pulse: Occasional irregularity (DD: Af, how?)

## Premature Atrial Contractions

### Definition

Premature discharge of an atrial ectopic focus

### ECG

- P waves: Abnormal (may be inverted)
- Normal QRS-complexes
- Incomplete compensatory pause



Treatment No Rx (Stop digitalis)

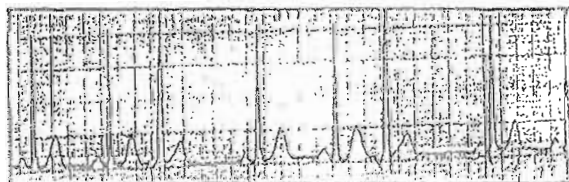
## Premature Junctional Contractions

### Definition

Premature discharge of junctional ectopic focus

### ECG

- P waves: Absent or inverted (before or after QRS)
- Normal QRS-complexes
- Complete compensatory pause



Treatment No Rx (Stop digitalis)

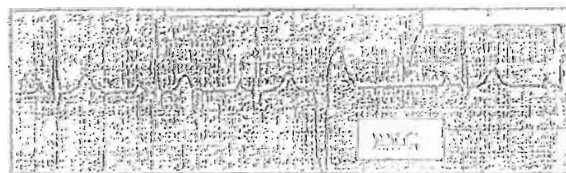
## Premature Ventricular Contractions

### Definition

Premature discharge of ventricular ectopic focus

### ECG

- Wide-bizarre QRS-complexes (No P wave)
- Complete compensatory pause
- It may be unifocal or multifocal
- They may be bigeminy or trigeminy
- They may be couplets or triplets



### Etiology + LQTS

### Indications of Rx

- |                   |                          |                            |
|-------------------|--------------------------|----------------------------|
| • Runs of PVCs    | • ↑↑ PVCs with exercises | • Underlying heart disease |
| • Multifocal PVCs | • R on T phenomenon      | • Symptomatic PVCs         |

### Treatment

Rx of the cause (Propranolol for LQTS)  
Lidocaine (Bolus + drip)

## Bradyarrhythmias

### Sinus Bradycardia

#### Description

- SAN discharges at lower rate for age ( $< 90/\text{min}$  in neonates &  $< 60/\text{min}$  in children)
- SAN is the pacemaker "Sinus rhythm"

#### Etiology

- Physiological: Sleep, athletes
- Pathological: Hypothyroidism, cholestasis, digitalis

#### ECG

- Bradycardia
- Sinus rhythm

#### Treatment

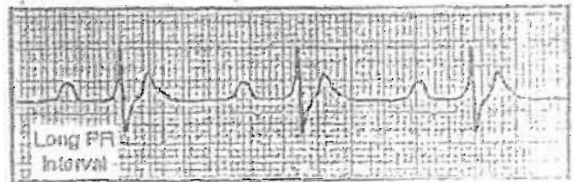
Rx of the cause (Atropine may be given)



## Heart Block

### First-Degree Heart Block

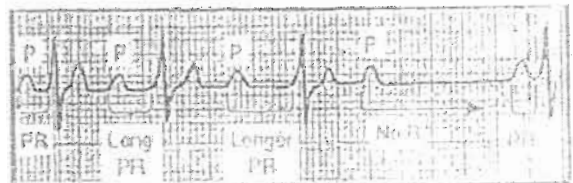
- $\uparrow\uparrow$  PR interval ( $N = 0.2$  sec in adults)
- No block
- Regular rhythm
- Digitalis effect, Rh carditis, myocarditis



### Second-Degree Heart Block

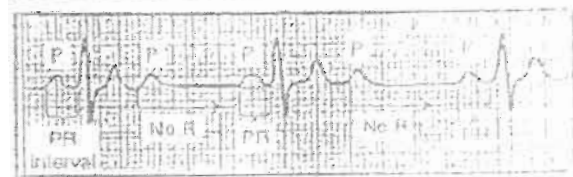
#### A) Mobitz type I (Wenckebach)

- Progressive  $\uparrow\uparrow$  PR interval till
- Non-conducted P wave then
- PR returns to normal & sequence is repeated



#### B) Mobitz type II

- Some P waves are not conducted (AV block)
- The block may be fixed (2:1, 3:1...) or variable



### Third-Degree Heart Block

- Complete absence of AV conduction
- Atria are controlled by the SAN
- Ventricles are controlled by idioventricular rhythm
- QRS-complexes are wide & bizarre
- Complete A-V dissociation



#### Etiology:

- Congenital: KSS, Maternal SLE, CHD
- Acquired: See before (Digitalis\*, postoperative\*)

#### Treatment:

- Rx of the cause: hypoxia, acidosis, shock...
- Atropin, Adrenaline, isoproterenol
- Cardiac pacing: Temporary or permanent

#### Indications of pacemaker:

- CHD with complete HB
- Stokes-Adam attacks
- Awake HR  $\leq 40/\text{min}$
- Prolonged pauses



## Precexcitation Syndromes

### Definition

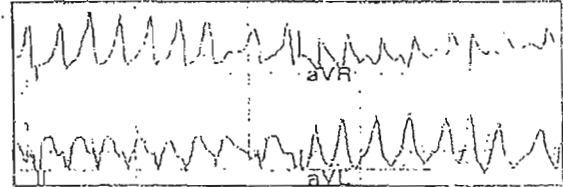
- Presence of accessory pathway allowing conduction between atria & ventricles other than the normal conductive system (AVN & AV bundle)
- Wolff-Parkinson-White syndrome is the most common type [Bundle of Kent]

### Clinical Picture

Patients with WPW are more prone to develop SVT

### ECG

- Short PR interval
- Delta wave (Initial slurring of the QRS-complex)
- Wide QRS-complex
- Diagnosis of ventricular enlargement can not be made with such ECG changes
- Propranolol
- Radiofrequency (or surgical) ablation of the accessory pathway



## Long Q-T Syndrome

### Definition

Disorder of myocardial repolarization characterized by prolonged QT interval on ECG & ventricular arrhythmias (usually torsades de pointes) that may lead to sudden death

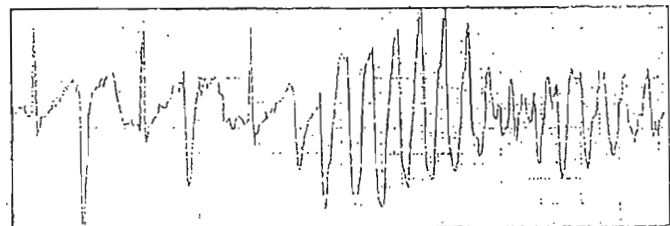
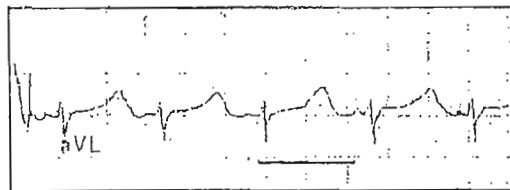
### Etiology

#### A) Congenital (*Defective ion channels*)

- Romano-Ward syndrome (AD)
- Lange-Nielsen syndrome (AR)
- Andersen syndrome (AD)

#### B) Acquired

- Antibiotics: Erythromycin
- Antifungal: Ketokonazole
- Antihistaminics: Terfenadine
- Electrolytes: Hypocalcemia
- Nutritional: Anorexia nervosa



### Clinical Picture

- Syncope (Often precipitated by exercises)
- Seizures
- Palpitation
- Sudden death

QT interval: from the onset of Q-wave to the end of T-wave

Not all patients with long QT have LQTS

### ECG

- Prolonged QT interval (> 0.47 sec is indicative, 0.44-0.47 sec is suspicious)
- QT is interpreted in relation to HR (Corrected QT interval)
- 24 hr-Holter monitoring

### Treatment

- Propranolol (Blunts HR response to exercises)
- ICD

## Common Anti-arrhythmic Drugs

Class	Indications	Dose	Side Effects
<b>Class IA</b>			
Quinidine sulfate	▪ SVT ▪ Atrial flutter	Oral 20-60 mg/Kg/day	▪ Nausea, vomiting ▪ Hemolytic anemia, $\downarrow\downarrow$ PLT
Quinidine gluconate	▪ AF ▪ VT		▪ SLE ▪ $\uparrow\uparrow$ QT interval
Procainamide	▪ SVT ▪ Atrial flutter ▪ AF ▪ VT	Oral 20-50 mg/Kg/day IV 3-6 mg/Kg (over 5 min)	▪ Nausea, vomiting ▪ Hemolytic anemia, $\downarrow\downarrow$ PLT ▪ SLE ▪ $\uparrow\uparrow$ QT interval
<b>Class IB</b>			
Lidocaine	▪ PVC ▪ VT ▪ VF	IV L: 1 mg/Kg M: 30-50 $\mu$ g/Kg/min	▪ Coma, Confusion ▪ Convulsions ▪ HB
Phenytoin	▪ Digitalis toxicity	Oral 3-8 mg/Kg/day IV 10-15 mg/Kg (1 hr)	▪ Gum hypertrophy, Generalized LN ▪ Aplastic anemia, Ataxia ▪ Pregnancy: Teratogenic, bleeding ▪ Vit. D deficiency, hirsutism ▪ Hypotension, bradycardia, HB
<b>Class IC</b>			
Flecainide	▪ SVT ▪ Atrial flutter, AF ▪ VT	Oral 3-10 mg/Kg/day	▪ Nausea ▪ Blurring of vision
<b>Class II</b>			
Propranolol	▪ SVT ▪ PVC ▪ LQT	Oral 1-4 mg/Kg/day IV 0.1 mg/Kg (5 min)	▪ Bronchospasm, Hypoglycemia ▪ Hypotension ▪ HF ▪ Bradycardia
<b>Class III</b>			
Amiodarone	▪ SVT (resistant) ▪ JET ▪ VT	Oral 10 mg/Kg/day (2 wks) 5 mg $\rightarrow$ 2.5 mg/Kg/day IV 3.5-5 mg/Kg (30 min)	▪ Hypothyroidism ▪ Hyperthyroidism ▪ Hepatotoxicity ▪ Pulmonary fibrosis
<b>Class IV</b>			
Digoxin $\uparrow\uparrow$ IC Ca, $\uparrow\uparrow$ Contractility	▪ SVT (Non WPW) ▪ Atrial flutter ▪ AF	Oral L: 40 $\mu$ g/Kg (1/2, 1/4, 1/4) M: 10 $\mu$ g/Kg/day IV 3/4 Oral dose	▪ Nausea, vomiting ▪ Blurring of vision, colored vision ▪ PAC, PVC, SVT, VT, Bradycardia ▪ Gynecomastia (prolonged use)
Verapamil	▪ SVT (Non WPW) ▪ Atrial flutter ▪ AF	Oral 2-7 mg/Kg/day IV 0.2 mg/Kg (CaCl ready)	▪ Bradycardia ▪ Hypotension ▪ HF ▪ HB
Adenosine	▪ SVT	IV	▪ Facial flushing ▪ Chest pain, Dyspnea ▪ Bradycardia ▪ Bronchospasm

## Diseases of the Myocardium

### Definition

Diseases affecting the cardiac muscle

### Etiology

#### 1. Familial/Hereditary

- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Iry Endocardial fibroelastosis
- Mitochondrial cardiomyopathy
- Carnitine deficiency (& FA oxidation defects)
- Muscular dystrophy (Duchene)
- Friedreich's ataxia

#### 2. Infection

- a. **Viral:** Coxsackievirus A&B, Adenovirus, EBV, MMR, VZ, HIV
- b. **Bacterial:** Diphtheria, Typhoid, TB, Sepsis
- c. **Fungal:** Histoplasmosis, actinomycosis
- d. **Rickettsial:** Rocky Mountain spotted fever
- e. **Parasitic:** Trypanosoma, Toxoplasmosis, Trichinosis (Trichinella spiralis), Bilharziasis

#### 3. Metabolic

- Fbry
- Hemochromatosis
- GSD
- MPS

#### 4. Nutritional

- Beriberi (Vit. B<sub>1</sub> deficiency)
- Selenium deficiency
- Kwashiorkor
- Hypercholesterolemia

#### 5. Endocrinal

- Hyperthyroidism
- Hypothyroidism
- Pheochromocytoma
- IDM

#### 6 Collagen-Vascular

- JRA
- SLE
- Dermatomyositis
- Scleroderma
- Vasculitis Syndromes
- Amyloidosis

#### 7. Drugs/Toxins

- Alcohol
- Adriamycin
- Irradiation
- Cyclophosphamide

#### 8. Coronary artery diseases

- a. **Congenital**
  - Abnormal origin
  - Abnormal course
- b. **Acquired**
  - Kawasaki disease
  - Vasculitis

#### 9. Hematological

- Anemia
- Thalassemia
- Sickle cell anemia
- Hemochromatosis
- Leukemia
- Idiopathic hypereosinophilic syndrome

#### 10. Chronic volume &/or pressure overload and arrhythmias

## Myocarditis

### Definition

- Inflammation of the myocytes due to Infectious\*, Toxic, Collagen-vascular diseases process with No coronary pathology.
- Myocarditis may be associated with pericarditis or endocarditis

### Etiology

- As before...
- Viral myocarditis is the commonest cause

## Viral Myocarditis

### Etiology

Coxsackievirus B, Adenovirus

### Pathogenesis

- ☑ Acute myocarditis: Direct tissue damage
- ☑ Chronic myocarditis: Immune-mediated damage → Dilated cardiomyopathy

### Clinical Picture

- Acute myocarditis (Usually in neonates):
  - Constitutional manifestations: FAHM
  - Acute onset of HF
  - Muffled heart sounds
  - Arrhythmias
  - High mortality rate
- Chronic myocarditis (Usually in older children):
  - Gradual onset of HF
  - Development of DCM
  - Spontaneous resolution in 10-50%, mortality rate = 50% within 2 yrs

### Investigations

#### A) Laboratory

- Cardiac enzymes (CK, LDH)
- ESR
- Viral studies: IgM

#### B) Imaging

- CXR
- ECG
- ECHO

#### C) Invasive

- Endomyocardial biopsy (Catheterization): Inflammation, PCR for viruses

### Treatment

1. Px of HF
2. Rx of arrhythmias
3. Steroids
4. IVIG (2 g/Kg/dose)
5. Cardiac transplantation

Digitalis should be given at half the dose, Why?
--

Steroids is <u>controversial</u> 2 mg/Kg/day
---

## Cardiomyopathy

	Dilated Cardiomyopathy	Hypertrophic Cardiomyopathy	Restrictive Cardiomyopathy
Etiology	<ul style="list-style-type: none"> <li>Idiopathic*</li> <li>Post-viral</li> <li>Familial (AD, AR, XL)</li> <li>?</li> <li>?</li> </ul> <p>Myocardial biopsy: Useful early in the disease</p>	<ul style="list-style-type: none"> <li>Idiopathic (IHSS)</li> <li>Idiopathic hypertrophic subaortic stenosis</li> <li>Familial (AD)</li> <li>Obstructive CHD (AS, Coarctation)</li> <li>IDM</li> <li>Steroids in BPD (Preterm)</li> <li>Metabolic (GSD, MPS)</li> </ul>	<ul style="list-style-type: none"> <li>Idiopathic</li> <li>Sarcoidosis</li> <li>Amyloidosis</li> <li>MPS</li> <li>Scleroderma</li> <li>Malignancy</li> <li>Idiopathic hypereosinophilic syndrome</li> </ul>
Genetics	50% AD, AR, XL	50% AD	??
Genes	Actin, myosin, dystrophin, troponin genes	Actin, myosin genes	??Unknown (Troponin)
Basic dysfunction	<ul style="list-style-type: none"> <li>↓↓ Contractility (↓↓ SV)</li> <li>Systolic dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>↓↓ Compliance (↓↓ Filling) "↑↑ Hypertrophy"</li> <li>Diastolic dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>↓↓ Compliance (↓↓ Filling)</li> <li>Diastolic dysfunction</li> </ul>
Ventricle affection	LV** (mainly)	LV***	RV > LV
C/P	<ul style="list-style-type: none"> <li>↓↓ CO</li> <li>Pulmonary congestion</li> <li>Systemic congestion</li> </ul>	<ul style="list-style-type: none"> <li>↓↓ CO</li> <li>Pulmonary congestion</li> <li>May be asymptomatic (accidental, murmur)</li> </ul>	<ul style="list-style-type: none"> <li>Marked atrial dilatation</li> <li>↓↓ CO</li> <li>Systemic congestion</li> <li>Pulmonary congestion</li> </ul>
General exam.	Hypotension; HF (edema, liver...)	Pulsus bisferiens	
Cardiac examination	<ul style="list-style-type: none"> <li>Biventricular enlargement</li> <li>Weak apex</li> <li>S<sub>3</sub> + Gallop</li> <li>MR, TR</li> </ul>	<ul style="list-style-type: none"> <li>LV enlargement</li> <li>Double apex</li> <li>S<sub>4</sub></li> <li>Ejection systolic murmur (↑↑ with standing)</li> </ul>	<ul style="list-style-type: none"> <li>RV enlargement (Late)</li> <li>RA &amp; LA enlargement (2-3 fold &gt; ventricles)</li> <li>S<sub>4</sub></li> <li>MR, TR</li> </ul>
Investigations [ECHO]	Dilated LV cavity Thin LV wall	Asymmetric concentric or apical LV hypertrophy	Normal or small ventricular cavity Marked atrial dilatation
Sudden Death	Yes (Arrhythmias); freq. ECG is needed	YES (1-11%/yr) even in asymptomatic...	(1.5%/yr)
Medical Rx	<ul style="list-style-type: none"> <li>HF: ACE inhibitor, Diuretics, Digitalis, β-adrenergic blockers (Carvedilol)</li> <li>Arrhythmias: Anti-arrhythmic drugs</li> <li>Anticoagulants</li> <li>Carnitine: May be useful</li> </ul>	<ul style="list-style-type: none"> <li>Avoid severe physical activity</li> <li>β-Blockers + Ca-channel blockers</li> <li>Pacemaker</li> <li>Arrhythmias: Anti-arrhythmic drugs</li> <li>Digitalis is CI, Why??</li> </ul>	<ul style="list-style-type: none"> <li>HF: ACE inhibitor, Diuretics, Digitalis</li> <li>Arrhythmias: Anti-arrhythmic drugs</li> <li>Anticoagulants</li> <li>Amrinone, Milrinone (Inotrope + VD)</li> </ul>
Surgical Rx	ICD Cardiac transplantation	ICD Cardiac transplantation Septal myotomy (Myectomy)	ICD Cardiac transplantation

## Hypertension

### Definitions

**Hypertension:** Systolic &/or diastolic BP > 95<sup>th</sup> % for age & sex on at least 3 occasions

**Pre-hypertension:** Systolic &/or diastolic BP between 90<sup>th</sup> & 95<sup>th</sup> % for age & sex

**White-coat hypertension:** Hypertension only in health care facilities

### Hypertensive crisis

**Hypertensive emergencies:** BP > 99<sup>th</sup> % with end organ damage

**Hypertensive urgencies:** BP > 99<sup>th</sup> % with No end organ damage

**Hypertensive encephalopathy:** BP > 99<sup>th</sup> % with headache, vomiting, visual, seizures,  
Focal neurologic deficits & DCL

**Accelerated, malignant HTN:** BP > 99<sup>th</sup> % with retinal changes (Papilledema, Hge...)

### Classification (*Giff with 40% of the circumference*)

#### A) Primary (Essential) HTN

- Unknown etiology
- May be related to obesity, genetic factors, diet or stress??
- Markers of development of subsequent HTN
  - Greater HR & BP responses to stress
  - Greater HR & BP responses to salt intake
  - ↑↑ Urinary catecholamines
  - ↑↑ RBC Na transport

#### Hypertensive emergencies:

- HTN encephalopathy
- ICH
- HTN Heart failure
- ARF
- Malignant HTN (Vascular)

	Primary (Essential) hypertension	Secondary hypertension
Frequency	Less	Much more common
Age	Adolescents	Any age (Including neonates)
Severity	Usually mild	Mild to Severe
Weight	Mild to moderate obesity	Marked obesity with Cushing
Family history	+Ve	-Vc
C/P of the cause	No	Present

#### B) Secondary HTN (*Curable causes*) *90% of cases* *Renoparenchymal dis* *Renal a. Stenosis* *Co A*

- Secondary to a specific etiology
- May be caused by renal, endocrinal, vascular, drugs, CNS causes
- Pathogenesis of secondary HTN: *Renovascular*

##### a. Renal causes\*\*

- ↑↑ Renin-Angiotensin system → Angiotensin II → VC
- ↑↑ Renin-Angiotensin system → Aldosterone → Na & water retention

##### b. Endocrinal causes

- Hyperthyroidism: ↑↑ HR *Systolic HTN*
- Hyperparathyroidism: ↑↑ Ca (VC)
- Cushing, CAH, Conn's: ↑↑ Mineralocorticoids
- Pheochromocytoma, Neuroblastoma: ↑↑ Catecholamines

##### c. Vascular causes

- Coarctation
- Vasculitis: VC & Renal affection

##### d. CNS causes *ATCP, Gullian barre*

##### e. Drugs & toxins

- Cocaine (VC)
- Tobacco (↑↑ Viscosity)
- OCPs (Salt & water retention)
- Sympathomimetics?? (VC & Inotropic)
- Lead (VC)
- Cyclosporine (Nephrotoxic)

## Etiology

### A) Transient or Intermittent HTN

Renal	CNS
APSGN ARF ATN HSP HUS Pyelonephritis Renal trauma	Autonomic neuropathy Guillain-Barre syndrome Familial Dysautonomia ↑↑ Intracranial Pressure Encephalitis Posterior fossa lesions Poliomyelitis
Drugs & Toxins	Others
Cocaine Tobacco Oral contraceptives Sympathomimetics (Nasal decongestants...) Lead Cyclosporine Steroids & ACTH Withdrawal of antihypertensives Vitamin D intoxication Licorice	Fractures Burns ECMO After repair of coarctation Hypercalcemia

### B) Chronic or persistent HTN

Renal	CNS
Chronic GN Chronic PN Congenital (MCDK, dysplasia, hypoplasia...) Collagen-vascular (SLE...) Reflux nephropathy Renal tumors	Intracranial masses Intracranial tumors Intracranial hemorrhage
Vascular	Endocrinal
Coarctation Renal artery stenosis (Neurofibromatosis...) Renal vein thrombosis Umbilical artery catheterization Vasculitis Takayasu arteritis Moyamoya disease	Hyperthyroidism Hyperparathyroidism Pheochromocytoma Neuroblastoma Cushing, CAH, Conn's Liddle's
	Essential HTN

### C) Common causes of HTN

Age Group	Common Causes
Neonates	Renal artery thrombosis, COA, BPD, Congenital renal anomalies
< 6 yrs	Renal parenchymal disease, COA, renal artery stenosis
6-10 yrs	Renal parenchymal disease, renal artery stenosis, primary HTN
> 10 yrs	Primary HTN, Renal parenchymal disease

## Clinical Picture

- HTN may be asymptomatic discovered only on routine examination
- Symptoms: Headache, blurring of vision, epistaxis, hypertensive crises...

## Approach to a case of Hypertension

### A) History:

- ☒ Symptoms of HTN?!
- ☒ History of hematuria, UTI, fever, drugs...
- ☒ Family history

### Methods of measurement:

- Auscultation
- Palpation
- Doppler
- Dinamap??

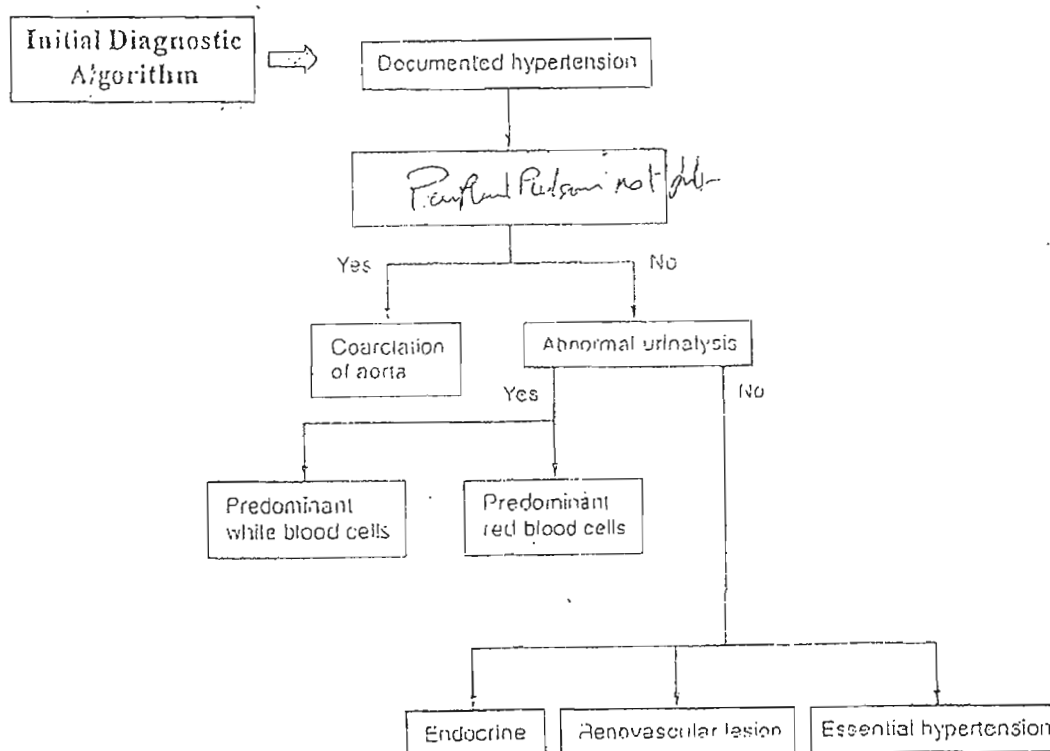
### B) Physical examination:

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> BP measurement (4 limbs)          | <input checked="" type="checkbox"/> Virilization                     |
| <input checked="" type="checkbox"/> Pallor                            | <input checked="" type="checkbox"/> Ambiguous genitalia              |
| <input checked="" type="checkbox"/> Fundus examination: Papilledema   | <input checked="" type="checkbox"/> Pericardial rub                  |
| <input checked="" type="checkbox"/> Turner (Webbing)                  | <input checked="" type="checkbox"/> Café-au-lait                     |
| <input checked="" type="checkbox"/> Cushing disease (Trunkal obesity) | <input checked="" type="checkbox"/> Skin rash (SLE, HSP, vasculitis) |
| <input checked="" type="checkbox"/> Proptosis                         | <input checked="" type="checkbox"/> Edema (Puffiness)                |
| <input checked="" type="checkbox"/> Goiter                            | <input checked="" type="checkbox"/> Abdominal mass                   |
| <input checked="" type="checkbox"/> Rickets, deformities              | <input checked="" type="checkbox"/> Neurologic deficits              |

### C) Investigations:

- ☒ Renal evaluation, Why?
- ☒ Renal Doppler & angiography
- ☒ PRA
- ☒ Renal vein PRA
- ☒ Cardiac evaluation (ECG, ECHO), Why?

uric a. Directly correlated to  
sys BP & Diastolic BP  
may have a role in future  
of Essential HTN





## Treatment

### A) Essential hypertension

1. Non-pharmacologic: Weight reduction, salt restriction, exercise, avoidance of smoking
2. Pharmacologic: Antihypertensive

### B) Secondary hypertension

Curable forms of HTN

1. Coarctation: Catheter or surgical correction
2. Tumors: Surgical Removal (Pheochromocytoma...)
3. Renovascular HTN: Balloon angioplasty, Surgical correction
4. Renal parenchymal diseases: Antihypertensive, nephrectomy (if unilateral pathology)

### C) Hypertensive Crisis

#### Definitions

#### Target

- ☒ Hypertensive emergency: Immediate controlled ↓↓ of BP (1hr)
- ☒ Hypertensive urgency: Rapid ↓↓ of BP (within hours)

#### Drugs used

- ☒ Labetalol
- ☒ Na Nitroprusside
- ☒ Diazoxide
- ☒ Nifedipine (SL)
- ☒ Furosemide
- ☒ Hydralazine

#### In General:

1/3 of the total planned reduction in the 1<sup>st</sup> 6hrs  
The remaining over the next 48-72 hrs

#### Subsequent management

- ☒ Shift to oral Rx
- ☒ Regular F/U

## Prognosis

- Essential HTN: Long life
- Transient HTN: Recovery
- Chronic untreated cases: Deterioration of renal & cardiac functions

## Anti-hypertensive Drugs

	Mechanism	Dose	Side Effects
<b>Arterial VD</b>			
Hydralazine (Aprisoline)	▪ Arteriolar VD	<u>IV</u> 0.1-0.4 mg/Kg/dose every 4-6 hr <u>PO</u> 1 mg/Kg/dose (6 hr)	▪ Tachycardia ▪ Nausea, vomiting ▪ Drug-induced SLE
Minoxidil	▪ Arteriolar VD	<u>PO</u> 5 mg/day (12-24 hr)	▪ Hypertrichosis
Nitroprusside (Nipride)	▪ Arteriolar* VD ▪ Venular VD	<u>IV Infusion</u> 0.5-10 µg/Kg/min	▪ Thiocyanate production ▪ Photochemical degradation??
Diazoxide (Hyperstat)	▪ Arteriolar VD	<u>Rapid IV</u> 3-5 mg/Kg/dose	▪ Tachycardia, hypotension ▪ Hyperglycemia
<b>Adrenergic #</b>			
Phentolamine	α-blocker	<u>IV</u> 0.1 mg/Kg/dose (1-2 hr)	▪ Tachycardia
Prazocin (Minipress)	α-blocker	<u>PO</u> 0.1 mg/Kg/dose (6 hr)	▪ Orthostatic hypotension
Propranolol (Inderal)	▪ β-blocker ▪ ↓↓ Renin	<u>IV</u> 0.1 mg/Kg/dose (6-8 hr) <u>PO</u> 1-4 mg/Kg/day (6-8 hr)	▪ Bronchospasm, Hypoglycemia ▪ Hypotension ▪ HF ▪ Bradycardia
Arenolol (Tenormin)	β-blocker	<u>PO</u> 1-2 mg/Kg/day (6-8 hr)	"
Clonidine (Catapres)	Central α <sub>2</sub> - blocker	<u>PO</u> 5-25 µg/Kg/day (8 hr)	▪ Sedation, Constipation ▪ Rebound withdrawal HTN
Labetalol (Trandate)	α & β blocker	<u>IV</u> 0.2-1 mg/Kg/dose (bolus) 0.2-2 mg/Kg/hr (Infusion) <u>PO</u> 1-4 mg/Kg/day (6-8 hr)	▪ Orthostatic hypotension ▪ Bronchospasm
<b>ACE Inhibitors</b>			
Captopril (Capoten)	↓↓ AT-II ↓↓ Aldosterone	<u>Oral</u> 0.1-6 mg/Kg/day (8 hr)	▪ Cough, rash, neutropenia ▪ Proteinuria, ↓↓ GFR, ↑↑ K
Enalapril (Vasotec)	Longer-acting	<u>Oral</u> 0.1-0.6 mg/Kg/day (24 hr)	▪ Hypotension
<b>Ca channel #</b>			
Nifedipine (Epilet)	Ca channel blocker	<u>Oral</u> 0.5-3 mg/Kg/day (12 hr)	▪ Tachycardia ▪ Facial flushing
Amlodipine (Norvasc)	Ca channel blocker	<u>Oral</u> 0.1-0.6 mg/Kg/day (24 hr)	▪ Tachycardia ▪ Facial flushing
<b>Diuretics</b>			
Furosemide			
Hydrochloro- thiazide /			
Bumetanide			
Spirolactone			

## Heart Failure

### Definition

Inability of the heart to maintain adequate CO to meet the metabolic needs of the body

### Etiology

#### A) According to the Pathophysiology

##### 1. Preload failure (Volume overload)

- ☒ Lt-to-Rt shunts: VSD, PDA, ASD
- ☒ Valve incompetence: MR, AR, TR
- ☒ Hypervolemia: ARF

##### 2. Afterload failure

- ☒ Obstructive lesions: AS, Coarctation
- ☒ Systemic & Pulmonary hypertension

##### 3. Contractility failure

- ☒ Cardiomyopathy
- ☒ Myocarditis

##### 4. Arrhythmic failure

- ☒ Extreme Tachycardia
- ☒ Extreme bradycardia
- ☒ Acute myocarditis: Direct tissue damage

##### 5. High CO failure (Hyperdynamic circulation)

- ☒ Anemia
- ☒ AVF *Vein of Galen*
- ☒ Thyrotoxicosis

High CO failure

- High CO But
- Inadequate CO

#### B) According to the Age

##### 1. Fetal

- ☒ Anemia: Rh incompatibility
- ☒ Arrhythmias: SVT, VT, Complete HB

##### 2. Preterm

- ☒ PDA, VSD
- ☒ Fluid overload ( $\uparrow\uparrow$  IVF)
- ☒ Hypertension
- ☒ BPD

##### 3. Term

- ☒ Truncus arteriosus & Single ventricle
- ☒ HLHS & Coarctation
- ☒ Acute viral myocarditis
- ☒ Hypoxic cardiomyopathy
- ☒ AV malformation (Vein of Galen)

Cranial Bruit

##### 4. Infants-Toddlers

- ☒ VSD
- ☒ Cardiomyopathy & myocarditis
- ☒ SVT

☒ HUS

☒ Kawasaki

☒ anomalous Lt coronary artery

##### 5. Children-Adolescents

- ☒ RHD
- ☒ Infective endocarditis
- ☒ Cardiomyopathy & myocarditis

☒ GN (HTN)

☒ Sickle cell anemia

☒ Thyrotoxicosis

## Clinical Picture

### a. Low CO

- Syncope
- Blurring of vision
- Easy fatigability
- Anginal pain
- Oliguria

### b. Systemic Congestion

- Anorexia, nausea, vomiting
- Dyspepsia, malabsorption
- Congested neck veins
- LL edema
- Hepatomegaly

### c. Pulmonary Congestion

- Cough, dyspnea, hemoptysis
- Recurrent chest infection
- Bilateral basal crepitations

### d. Cardiac examination

- Cardiomegaly (Exception...)
- Gallop
- Murmurs

Ankle edema commonly seen in adults is Not found in infants

Examination of JVP is of little use in infants

#### HF in Infants:

- Tachycardia
- Tachpnea
- Tender hepatomegaly
- Others: FTT, poor feeding...

Sweating is an important sign

## Investigations

### A) Laboratory

- Electrolytes (↓↓ Na, ↓↓ K)
- Blood gases (Metabolic acidosis, respiratory alkalosis)
- B-type natriuretic peptide: ↑↑

### B) Imaging

- CXR
- ECG
- ECHO

### C) Invasive

- Endomyocardial biopsy (Catheterization): Cardiomyopathy & myocarditis

## Clinical Grading

	Acute Congestive HF	Chronic Congestive HF
Grade I	HF	Exertional dyspnea
Grade II	HF + Pulmonary edema	Exertional dyspnea + systemic congestion
Grade III	HF + Cardiogenic shock	Dyspnea at rest + ↑↑ systemic congestion

## New York Heart Association Functional Classification

NYHA

	Manifestations
Class I	Asymptomatic
Class II	Dyspnea with moderate activity
Class III	Dyspnea with mild activity
Class IV	Dyspnea at rest

## Treatment

### A) General

1. Rest
2. Positioning: Semi-setting
3. Oxygen: How??
4. Sedation: Chloral hydrate, phenobarbitone, morphine
5. Diet:
  - ↑↑ Calories
  - ↓↓ Salt (Breast milk or low Na formula)
  - NGT may be needed (Tachypnea)
  - IVF (Glucose Not saline + Proper calculation 60-70%)
6. Metabolic abnormalities (↓↓ Ca, ↓↓ glucose)
7. Rx of Infection (Respiratory)
8. Rx of Anemia (Packed RBC)
9. Rx of the cause (Rheumatic activity, Arrhythmias, HTN)
10. Rx of precipitating factors (Infective endocarditis)

### B) Medications

#### 1. Preload Reducing agents (Diuretics)

	Mechanism	Dose	Side effects
Furosemide (Lasix) Used with markedly ↓↓ KFT	Loop diuretic (# NaK <sub>2</sub> Cl)	<u>IV</u> 1 mg/Kg/dose (4-6 hr) <u>PO</u> 1-4 mg/Kg/day (6-12 hr)	▪ Hypokalemia (Add K-syr up) ▪ Alkalosis ▪ Hyponatremia ▪ Hypovolemia
Hydrochloro- thiazide	DCT (# NaCl)	<u>PO</u> 2-4 mg/Kg/day (8-12 hr)	▪ Hypokalemia (Add K-syr up) ▪ Alkalosis
Spironolactone	Collecting ducts (# aldosterone)	<u>PO</u> 1-3 mg/Kg/day (8-12 hr)	▪ Hyperkalemia ▪ Gynecomastia
Bumetanide	50 times > furosemide	<u>IV</u> 0.01 mg/Kg/dose (4-6 hr) <u>PO</u> 0.01 mg/Kg/day (6-12 hr)	As furosemide

#### 2. Afterload Reducing agents (Dilators)

	Mechanism	Dose	Side effects
Captopril (Capoten)	↓↓ AT-II ↓↓ Aldosterone	<u>Oral</u> 0.1-6 mg/Kg/day (8 hr)	▪ Cough, rash, neutropenia ▪ Proteinuria, ↓↓ GFR, ↑↑ K
Enalapril (Vasotec)	Longer-acting ACE inhibitor	<u>Oral</u> 0.1-0.6 mg/Kg/day (24 hr)	▪ Hypotension
Prazocin (Minipress)	α-blocker	<u>PO</u> 0.1 mg/Kg/Dose (6 hr)	▪ Orthostatic hypotension
Hydralazine (Apresoline)	▪ Arteriolar VD	<u>IV</u> 0.1-0.4 mg/Kg/dose every 4-6 hr <u>PO</u> 1 mg/Kg/dose (6 hr)	▪ Tachycardia ▪ Nausea, vomiting ▪ Drug-induced SLE
Nitroprusside (Nipride)	▪ Arteriolar*VD ▪ Venular VD	<u>IV Infusion</u> 0.5-10 µg/Kg/min	▪ Thiocyanate production ▪ Photochemical degradation
Nitroglycerin (Tridil)	▪ Venular*VD ▪ Arteriolar VD	<u>IV Infusion</u> 1-20 µg/Kg/min	▪ Hypotension
Amrinone	VD + Inotropic	1-20 µg/Kg/min	▪ Hypotension

### 3. $\beta$ -adrenergic blockers: Carvedilol

- ☒  $\uparrow\uparrow$  exercise tolerance
- ☒  $\downarrow\downarrow$  Hospitalization
- ☒  $\downarrow\downarrow$  Mortality

$\beta$ -adrenergic blockers Should  
Not be used in acute HF

### 4. Phosphodiesterase inhibitors (VD + Inotropic)

- a. Amrinone: 1-20  $\mu\text{g/Kg/min}$
- b. Milrinone

### 5. Digitalis

Nature: Cardiac glycoside

Absorption: Duodenum

Excretion: Renal  $\Rightarrow$

Action:

- $\uparrow\uparrow$  Contractility
- $\uparrow\uparrow$  Excitability
- $\downarrow\downarrow$  Conductivity
- $\downarrow\downarrow$  Automaticity
- Diuretic effect

Adjust the dose in patients  
with renal impairment

Digitalis has a narrow safety margin

Indications:

- HF (With impaired contractility; FS < 28%)
- Atrial arrhythmias

Dose:

#### a. IV route

- Digitalizing dose: 0.04 mg/Kg divided into 3 doses (1/2, 1/4, 1/4) every 8 hrs
- Maintenance: 0.01 mg/Kg divided into 2 equal daily doses (every 12 hrs)

#### b. Oral route

- No initial digitalization (Digitalization is usually achieved within 7-10 days)
- Maintenance: 0.01 mg/Kg divided into 2 equal daily doses (every 12 hrs)



0.25

Toxicity:

- a. GIT: Nausea, anorexia, vomiting, diarrhea,
- b. CNS: Headache, visual disturbance (colored vision)
- c. CVS:
  - Bradycardia, Heart block
  - Extrasystoles, AF, atrial flutter, SVT
- d. Allergy, gynecomastia

Digitalis Effect

- Sagging depression of ST
- Inverted or flat T-wave
- $\uparrow\uparrow$  PR interval

Factors that may  $\uparrow\uparrow$  Digitalis Toxicity:

- Hypokalemia & hypercalcemia
- Diuretics (Furosemide, thiazides)
- Sympathomimetics, verapamil,  $\beta$ -blockers
- Renal impairment
- Preterm infants
- Myocarditis (Rheumatic & viral)
- Hypoxia, postoperative period

Treatment of Digitalis Toxicity:

- STOP digitalis
- Correction of hypokalemia & hypercalcemia
- Rx of arrhythmias: Phenytoin & lidocaine

Indications of measurement of digoxin level:  $\Rightarrow$

Monitoring of patient on Digitalis Rx:

Indications of serum level:

- Toxicity
- Inadequate response
- Renal impairment
- Accidental ingestion

## 5. Positive Inotropes

▫ Indications: Cardiogenic shock

▫ Drugs used:

	Supplied as	Dose
Dopamine	200 mg/5 ml	5-20 µg/Kg/min
Dobutamine	250 mg/5 ml	5-20 µg/Kg/min
Adrenaline	1 mg/1 ml	0.05-2 µg/Kg/min
Isoproterenol	1 mg/5 ml	0.05-2 µg/Kg/min

### ▫ Administration

- ICU (Monitoring...)
- Infusion or syringe pump
- Avoid sudden stoppage (Gradual withdrawal)
- Invasive monitoring is very helpful

### ▫ Some Notes

#### 1. Isoproterenol

- Sympathomimetic ( $\beta_1$ ,  $\beta_2$ )
- Inotropic + VD
- Side effects: Tachycardia, Hypotension, Arrhythmias

#### 2. Dopamine

- Sympathomimetic (Dopamine,  $\beta$ ,  $\alpha$ -receptors); according to the dose:
  - Small dose (2-5 µg/Kg/min): ↑↑ Renal blood flow
  - Moderate dose (5-10 µg/Kg/min): Inotropic
  - Large dose (> 10 µg/Kg/min): VC
- Less tachycardia than isoproterenol

Dopamine is incompatible with Ca & NaHCO<sub>3</sub>

#### 3. Dobutamine

- Sympathomimetic ( $\beta_1$ )
- Inotropic + mild VD
- Minimal effect on HR (the least arrhythmogenic one)
- Dobutamine is the preferable initial Rx if tachycardia is prominent
- Dopamine + Dobutamine is the commonest combination (↓↓ Dose of each)

Dobutamine has less chronotropic effect

#### 4. Adrenaline

- Sympathomimetic ( $\alpha$  &  $\beta$ -receptors)
- Inotropic + VC
- Side effects: ↓↓ Renal blood flow

## Practical Management of HF

- Start medical Rx with diuretics (Lasix) & VD (Captopril)
- Restrict digoxin to those with impaired contractility
- Give dopamine or dobutamine in cases of cardiogenic shock

## Daily F/U examination of admitted cases of HF

- Vital signs: HR (      ), BP (      ), RR (      )
- Liver
- Cardiac apex

## Infective Endocarditis

### Definition

Infection of the endocardial surface of the heart or the intimal surface of BV (PDA, COA)

### Etiology

#### A) Organism

##### ☒ Bacterial:

- Streptococcus viridans (50%)
- Staphylococcus aureus (40%)
- Enterococci (GIT & GU)
- Pseudomonas (IV drug use)
- CONS (Central vein)
- H.influenza
- HACEK: H.parainfluenza, Actinobacillus, Cardiobacterium, Eikenella & Kingella

Staph. aureus is the most common organism affecting normal heart!

##### ☒ Fungal

- Candida
- Aspergillus
- Histoplasma

Non-infective endocarditis  
 " Rheumatic fever  
 " SLE (Libman-Sacks)

##### ☒ Viruses

#### B) Patient

##### ☒ Cardiac lesion

##### ➤ High-risk category

- Complex cyanotic heart disease: TOF, TGA, Single ventricle
- Prosthetic valves
- Surgically constructed systemic to pulmonary artery shunt or conduit
- Repaired CHD with residual defects
- Previous infective endocarditis

##### ➤ Moderate-risk category

- Most other CHD (VSD, PDA, primum ASD, COA)
- RHD
- MVP with MR

##### ➤ Negligible-risk category

- Secundum ASD
- Repaired VSD & PDA (> 6m)
- Pacemakers & ICD
- MVP without regurge
- Coronary artery bypass

##### Negligible risk

(No prophylaxis)

- Secundum ASD
- Repaired VSD & PDA (> 6m)
- Pacemakers & ICD
- MVP without regurge
- Coronary artery bypass

##### ☒ Others

- Immunodeficiency
- Central venous catheters
- IV Drug abusers

#### C) Route

- ☒ Dental procedures
- ☒ Adenotonsillectomy
- ☒ Non-sterile instrumentation of GIT or GU systems
- ☒ Open heart surgery
- ☒ Central venous catheters



## Clinical Picture

### A) General manifestations

1. Fever, chills
2. Anorexia, Pallor & loss of weight
3. Pulse: Tachycardia, absent pulsations (Embolization)
4. Eye: Conjunctiva (Petichiae), Retina (Roth spots), Sudden blindness (Embolization)
5. Hands
  - Clubbing
  - Osler's nodules: Pulp of fingers
  - Splinter hemorrhages: Under the nails
  - Janeway lesions: Blue-red macules over palms & soles
6. Splenomegaly (70%)
7. Arthralgia & myalgia
8. Renal: Post-infectious GN (Hematuria)
9. CNS: Embolic hemiplegia, ICH

#### When to suspect

- Patient
- Predisposing factors
- C/P



### B) Cardiac manifestations

1. Feature of the underlying cardiac disease
2. Appearance of a new murmur (Sea-gull murmur?)
3. Change in the character of an already present murmur
4. HF, Why?? *Myocardial stress*

#### Causes of HF in IE

- Valve damage
- Myocarditis
- Fever

## Investigations

### A) Laboratory

- Blood culture (Repeated 3-5 times after proper skin decontamination)
- CBC, ESR, CRP
- C<sub>3</sub>, C<sub>4</sub>
- Electrolytes, KFTs
- Urine analysis



### B) Imaging

- CXR
- ECG
- ECHO

#### Value of ECHO in IE

- Diagnosis of 1<sup>st</sup> lesion
- Vegetations
- Cardiac evaluation (FS % ...)
- Detection of valve affection

Absence of vegetations does Not exclude infective endocarditis

## Duke Criteria

Major Criteria	Minor Criteria
≥ Positive blood culture	Predisposing factors
Evidence of endocarditis on ECHO:	Single Positive blood culture
▪ Vegetations	Fever
▪ New valvular regurge	Embolic manifestations
	Immune complex diseases (GN, arthritis, osler...)

### Interpretation of Duke Criteria

#### Definite Infective Endocarditis

- TWO major
- ONE major + THREE minor
- FIVE minor

#### Possible Infective Endocarditis

- ONE major + ONE minor
- THREE minor

## Prevention

Prevention is more important than Rx

A) Maintenance of good oral hygiene (More important than antibiotic prophylaxis)

B) Cardiac lesions requiring prophylaxis (According to level of risk)

C) Procedures requiring prophylaxis (Based on the risk of bacteremia)

	Procedures requiring prophylaxis	Procedures Not requiring prophylaxis
Dental	<ul style="list-style-type: none"> <li>▪ Tooth extraction</li> <li>▪ Root canal instrumentation</li> <li>▪ Surgery</li> <li>▪ LA (Intraligamentary)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Fluoride Rx</li> <li>▪ Filling cavities</li> <li>▪ Radiographs</li> <li>▪ LA (Non-Intraligamentary)</li> </ul>
Respiratory	<ul style="list-style-type: none"> <li>▪ Tonsillectomy</li> <li>▪ Adenoidectomy</li> <li>▪ Rigid bronchoscopy</li> </ul>	<ul style="list-style-type: none"> <li>▪ ETT</li> <li>▪ Grommet's tube</li> <li>▪ Flexible bronchoscopy</li> </ul>
GIT	<ul style="list-style-type: none"> <li>▪ Sclerotherapy for varices</li> <li>▪ Esophageal dilatation (Stricture)</li> <li>▪ Surgery involving the intestinal mucosa</li> </ul>	<ul style="list-style-type: none"> <li>▪ Endoscopy (± Biopsy)</li> <li>▪ TEE</li> </ul>
GU	<ul style="list-style-type: none"> <li>▪ Cystoscopy</li> <li>▪ Circumcision</li> <li>▪ VD, CS, IUD, D&amp;C</li> <li>▪ Urethral catheter</li> </ul>	
Others		<ul style="list-style-type: none"> <li>▪ Cardiac catheter</li> <li>▪ Pacemakers &amp; ICD</li> </ul>

### D) Antibiotic prophylaxis

#### 1. Oral, Respiratory & Esophageal

☒ Rational: Streptococcus viridans

☒ Drugs

	Agent	Regimen	
		Dose	When?
Most patients	Oral Amoxicillin	Single dose 50 mg/Kg	1 hour before procedure
Unable to take PO	IM/IV Ampicillin	Single dose 50 mg/Kg	30 min before procedure
Allergy to penicillin	Oral Azithromycin	Single dose 15 mg/Kg	1 hour before procedure
	Oral Cephalexin	Single dose 50 mg/Kg	1 hour before procedure
	Oral Clindamycin	Single dose 20 mg/Kg	1 hour before procedure
Allergy to penicillin & Unable to take PO	IV Clindamycin	Single dose 20 mg/Kg	30 min before procedure

#### 2. GU & Non-esophageal GIT

☒ Rational: Enterococci

☒ Drugs

	Agent	Regimen	
		Dose	When?
High-risk patients Before & After	IM/IV Ampicillin & IM/IV Gentamicin	50 mg/Kg/dose + 1.5 mg/Kg/dose	30 min before procedure
	IM/IV Ampicillin or Oral Amoxicillin	25 mg/Kg/dose	6 hour after procedure
High-risk patients & Allergy to penicillin	IV Vancomycin & IM/IV Gentamicin	20 mg/Kg (over 1-2 hr) + 1.5 mg/Kg/dose	30 min before procedure
Moderate-risk patient	IM/IV Ampicillin	50 mg/Kg/dose	30 min before procedure

## Treatment

### A) Medical

- Initial empirical therapy
  - Crystalline penicillin 200,000-300,000 U/Kg/day divided every 4-6 hrs for 4 wks
  - Crystalline penicillin + Gentamicin 3 mg/Kg/day divided every 12 hrs for 2 wks
  - Crystalline penicillin + Ceftriaxone 100 mg/Kg/day once daily for 2 wks
  - Ceftriaxone + Gentamicin 3 mg/Kg/day for 2 wks
- Culture positive: Specific antibiotic therapy according to the result
  - Staphylococcus: Oxacillin 200 mg/Kg/day divided every 6 hr + Gentamicin for 6 wks
  - Staphylococcus: Vancomycin 30 mg/Kg/day divided every 12 for 6 wks
  - Enterococci: Ampicillin 300 mg/Kg/day divided every 6 hr + Gentamicin for 6 wks
  - HACEK: Ceftriaxone 100 mg/Kg/day once daily for 4 wks
  - Fungal infection: Amphotericin B

### B) Surgical

1. Removal of vegetation & Valve replacement
  - Intractable HF
  - Prosthetic valve
  - Fungal IE
  - Failure of medical Rx
  - Myocardial abscess
2. Surgical repair
  - Rupture aortic sinus
  - Rupture mycotic aneurysm

## Complications

- ▣ Mortality = 25%
- ▣ HF
- ▣ HB
- ▣ Acquired VSD
- ▣ Embolization
- ▣ Rupture aortic sinus
- ▣ Rupture mycotic aneurysm
- ▣ Immune-complex disease: GN
- ▣ Meningitis, arthritis

## Shock

(Circulatory Failure)

### Definition

Inadequate tissue perfusion through the microcirculation with impaired cellular metabolism

### Etiology

Type	Causes	Notes
Septic	1. Primary (No focus) 2. Secondary (Serious focal infection) 3. Gut barrier failure (Bacterial translocation)	• G-ve (endotoxins)* • Clinical diagnosis
Hypovolemic	1. Hemorrhage 2. Dehydration (GE) 3. Burns 4. $\downarrow\downarrow$ Effective plasma volume	• Most common • Dramatic response to volume expansion
Obstructive	1. Tension pneumothorax 2. Cardiac tamponade 3. Cardiac obstructive lesions (AS, PS)	• No response to volume expansion
Cardiogenic	1. Acute HF (myocarditis, arrhythmias) 2. Late septic shock	• No response to volume expansion
Kinetic (Distributive)	1. Anaphylaxis (Drugs, insect bite) 2. Neurogenic (Vasovagal attack) 3. Early septic shock	• Due to VD $\rightarrow$ Relative hypovolemia
Mixed	1. TRA (hypovolemic, neurogenic, obstructive) 2. GE (hypovolemic, septic)	
Changing	1. Septic shock ▪ Early: kinetic (distributive) ▪ Late: cardiogenic (myocardial dysfunction) 2. Any type ▪ Late: gut failure "septic shock"	

### Pathophysiology (Body response to $\uparrow\uparrow$ ABP & tissue perfusion of vital organs)

1. Venous VC  $\rightarrow$   $\uparrow\uparrow$  VR
  2. Arteriolar VC  $\rightarrow$   $\uparrow\uparrow$  Peripheral resistance
  3.  $\uparrow\uparrow$  HR &  $\uparrow\uparrow$  SV  $\rightarrow$   $\uparrow\uparrow$  CO
  4.  $\uparrow\uparrow$  ADH  $\rightarrow$  VC
  5.  $\downarrow\downarrow$  Renal perfusion  $\rightarrow$   $\uparrow\uparrow$  Renin-angiotensin system  $\rightarrow$   $\uparrow\uparrow$  AT-II  $\rightarrow$   $\uparrow\uparrow$  Aldosterone & VC
- } Mediated by  $\uparrow\uparrow$  sympathetic nervous system

### Clinical picture (4 clinical stages)

- C/P of the cause (GE, flushing, urticaria, stridor,  $\downarrow$  air entry, )

	Clinical Stage	Events	Clinical picture
I	Early Shock	Peripheral hypoperfusion	• Tachycardia • Poor peripheral perfusion (??)
II	Established Shock	Arterial hypotension	Above + Arterial hypotension
III	Advanced Shock	Vital organ hypoperfusion	Multiple organ system failure (MOSF) (??)
IV	Irreversible Shock	Irreversible cellular damage	Refractory metabolic acidosis

#### Poor peripheral perfusion:

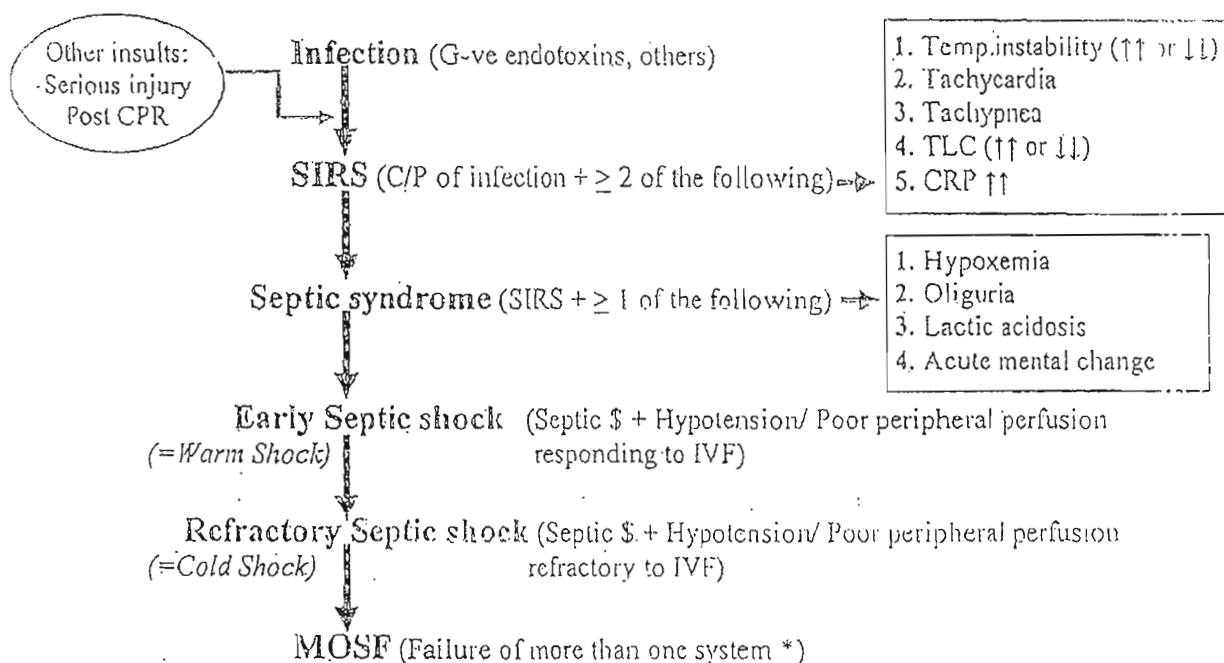
1. Cold extremities
2. Cyanosis
3. Core-Peripheral Temp.  $> 2^\circ\text{C}$
4. Capillary refill  $> 5$  seconds

#### MOSF:

- Failure of more than one system (ARF, ARDS, FHF, DIC, HIE)
- It occurs also in serious injuries & post-CPR

Organ	Manifestation	Management (Multisystem support)
Kidneys	ARF*	Urine output, Volume expander, Dopamine, Fluid balance
Lungs	Adult RDS (ARDS)*	O <sub>2</sub> , ETT, CPAP, M ventilation
GIT	Stress ulcers, He & gut failure	Antacids, NPO, cold stomach wash
Liver	Fulminant hepatic failure (FHF)*	Fluid, nutrition, Brain edema, Flumazenil
Blood	DIC*	FFP, PLT, Vitamin K ± Heparin
Metabolic	Metabolic acidosis & electrolyte #	↑↑ of acidosis, ↑↑K, ↓↓Ca, Temp. #
Brain	Hypoxic ischemic encephalopathy*	Care of the comatose: (10 items)
Heart	Myocardial ischemia & arrhythmias	ECG of arrhythmias

### Progression of Infection to SIRS



**SIRS = Systemic Inflammatory Response Syndrome**

**Etiology:** Severe infection

Other clinical insults (Major trauma, post CPR)

**Pathogenesis:** Massive inflammatory response with systemic activation of leucocytes & release of mediators

**Mediators:** Primary: TNF, IL-1, IL-6, IFN

Secondary: PAF, Leukotrienes

Anti-inflammatory: IL-4, 10, 11, 13 (Compensatory anti-inflammatory response \$)

### Management

- A) Monitoring
- B) Cardiovascular support
- C) Multisystem support
- D) Specific treatment

## A) Monitoring

### a. Clinical:

- Vital signs: HR, RR, BP, Temperature
- Peripheral perfusion: 4C
- Level of consciousness: HIE
- Urine output: Oliguria
- O<sub>2</sub> Saturation: Pulse oximeter

### b. Laboratory

- ABG: Metabolic acidosis
- Electrolytes: Na, K, Ca
- Blood glucose: Stress hyperglycemia
- KFTs: ARF
- Hb, Hct, PLT, PT, PTT: DIC
- Sepsis screen: (CBC, CRP, Blood culture)

### c. Imaging

- CXR: Pneumothorax, ARDS
- Echocardiography: Tamponade, Fraction shortening (FS) to evaluate contractility
- Doppler echocardiography: Non-invasive method of CO assessment

### d. Invasive

- Central Venous Pressure (CVP): "Normally = 1-5 cm H<sub>2</sub>O"
  - ☒ ↑↑ in cardiogenic shock, obstructive shock (pneumothorax, tamponade) & volume overload
  - ☒ ↓↓ in hypovolemic shock
- Pulmonary artery pressure (PAP)
- Pulmonary capillary Wedge pressure (PCWP)

## B) Cardiovascular support

### a. Oxygen therapy: (essential to prevent myocardial hypoxia & fatal arrhythmias)

- Method: Mask, prongs, CPAP, IMV, CMV
- Monitoring: Color, pulse oximeter, ABG

### b. Preload augmentation

- Indicated in all types of shock
- Fluid used:
  - Crystalloids: Saline or Ringers lactate (20 cc/Kg over 10-15 min, can be repeated)
  - Colloids: Albumin or plasma (10 cc/Kg over 15 min, ↑↑ Oncotic pressure)
  - Blood: Hemorrhagic shock
- Failure of response:
  - Cardiogenic shock
  - Obstructive shock
  - Ongoing losses (Internal Hge)



▫ CXR  
▫ Echocardiography

## c. Contractility Augmentation (+ve Inotropes)

## ▪ Indications:

- Cardiogenic shock
- Late septic shock
- Shock not responding to volume expansion

## ▪ Drugs used:

	Supplied as	Dose
Dopamine	200 mg/5 ml	5-20 µg/Kg/min
Dobutamine	250 mg/5 ml	5-20 µg/Kg/min
Adrenaline	1 mg/1 ml	0.05-2 µg/Kg/min
Isoprenalol	1 mg/5 ml	0.05-2 µg/Kg/min

## ▪ Administration

- ICU (Monitoring)
- Infusion or syringe pump
- Avoid sudden stoppage (Gradual withdrawal)
- Invasive monitoring is very helpful

## d. Afterload Reduction (Vasodilators)

## ▪ Indications:

- Cardiogenic shock not adequately responding to inotropic agents
- Along with adrenaline to counteract its undesirable VC effects

## ▪ Drugs used:

	Supplied as	Dose	Comment
Nitroprusside	50 mg/2 ml	0.5-10 µg/Kg/min	Arterial > Venous VD
Nitroglycerin	50 mg/10 ml	1-20 µg/Kg/min	Venous > Arterial VD
Amrinone	100 mg/20 ml	1-20 µg/Kg/min	VD + Inotropic

## e. Rx of arrhythmias:

- Correction of hypoxia, acidosis, electrolyte disturbances
- Bradyarrhythmias: Atropine & isoprenalol
- Tachyarrhythmias: Adenosine
- Ventricular arrhythmias: Lidocaine

C) Multisystem support (see before)D) Specific treatment

## a. Septic shock

- Sepsis screen
- Parenteral antibiotics (Ampicillin + 3<sup>rd</sup> generation cephalosporin)

## b. Hypovolemic shock

- Rx of dehydration (Deficit therapy)
- Stoppage of bleeding

## c. Obstructive shock

- Pneumothorax (IC tube) & Cardiac tamponade (Pericardiocentesis)
- Critical AS or PS (PG<sub>1</sub> can be used in duct-dependent lesions)

## d. Cardiogenic shock

- Rx of arrhythmias
- Rheumatic carditis (Steroids)

## e. Kinetic shock (Anaphylaxis)

- Adrenaline (IM)
- Others: Antihistaminics,  $\beta_2$ -agonists, O<sub>2</sub>, Steroids

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Question: 152

A newborn female has loose neck skin (Item Q152A) and nonpitting edema of the lower extremities (Item Q152B).

Of the following, the MOST appropriate evaluation for this infant is

- A. blood chromosome analysis
- B. magnetic resonance imaging of the brain
- C. slitlamp ophthalmologic examination
- D. ultrasonography of the liver
- E. voiding cystourethrography



American Academy  
of Pediatrics



2007 PREP SA on CD-ROM

Question: 157

You are evaluating a newborn boy who has lax abdominal musculature (Item Q157A) and bilateral undescended testes. Other findings on physical examination are normal.

Of the following, the MOST likely urologic abnormality in this boy is

- A. hydronephrosis
- B. renal cysts
- C. ureterocele
- D. ureteropelvic junction obstruction
- E. vesicoureteral reflux

American Academy  
of Pediatrics



2007 PREP SA on CD-ROM

Question: 167

You are seeing a 6-week-old infant who was born with trisomy 21 and a large atrioventricular septal defect. Over the previous week, she has tired with feeding and has not gained weight. Her respiratory rate is 60 breaths/min and heart rate is 150 beats/min. Auscultation reveals mild retractions and a 2/6 systolic murmur with a gallop rhythm. The liver is palpable at 2 cm below the costal margin, and the perfusion is good. You decide to increase the caloric content of the formula to 24 kcal/oz, and you contact her pediatric cardiologist to discuss referral for surgical repair.

Of the following, the BEST therapeutic option while awaiting surgical repair is

- A. captopril
- B. furosemide
- C. hydralazine
- D. propranolol
- E. verapamil

American Academy  
of Pediatrics



2007 PREP SA on CD-ROM

Question: 168

Numerous therapeutic agents are known to have teratogenic effects on the developing fetus.

Of the following, the findings in the newborn that are MOST suggestive of prenatal exposure to an angiotensin-converting enzyme inhibitor are

- A. deafness and cataracts
- B. microtia and conotruncal malformation
- C. nasal hypoplasia and stippled epiphyses
- D. neonatal anuria and patent ductus arteriosus
- E. smooth philtrum and lip

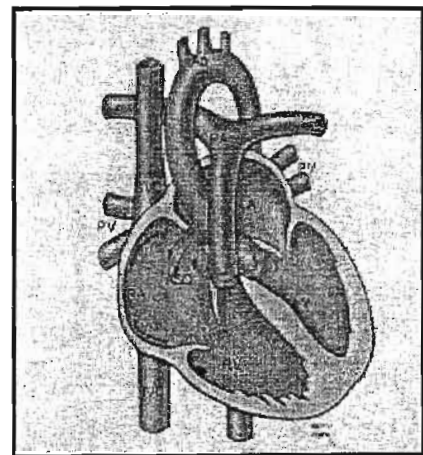
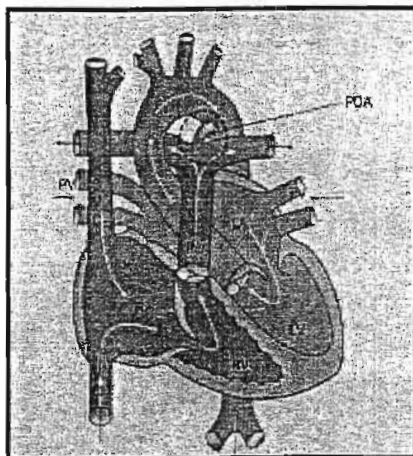


## Question: 179

An infant is born following a pregnancy complicated by no prenatal care and reduced fundal height for gestation on examination during labor. Fetal heart rate tracings are nonreassuring. Physical examination of the infant reveals a birthweight of 1,800 g, flattened facies (Item Q179A), low-set ears, respiratory distress, a large flank mass on the left, and joint contractures. Renal ultrasonography documents a single left multicystic and dysplastic kidney; the right kidney is absent.

Of the following, the BEST explanation for these findings is

- A. Alport disease
- B. congenital nephrotic syndrome
- C. congenital Wilms tumor
- D. oligohydramnios sequence
- E. Turner syndrome



# Clinical Pediatrics

By

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2010

# History

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## A) Personal History

Name, Age, Sex, Residence

## B) Complaint

No medical terms

## C) Present History

- Analysis of the complaint: Onset, Course, Duration
- Other symptoms of the same systems: Cardiac, Hematologic...
- Other symptoms of other systems
- Investigations
- Treatment

## D) Past History

- Past history of similar diseases
- Hospitalization
- Chronic diseases

## E) Developmental History

- Motor development
- Mental development

## F) Perinatal History

### 1. Antenatal

- HTN, DM
- Drugs, Radiation
- Congenital infections: Fever, Rash
- Investigations: US

### 2. Natal

- Duration: Term, Preterm
- Mode of delivery: VD or CS (Why?)
- Obstructed labor: How??
- Instrumental delivery
- Immediate crying, cyanosis

### 3. Postnatal (Neonatal):

- Jaundice, Cyanosis, Convulsions
- Feeding, RD
- NICU admission: (Why? How long? Diagnosis)

## G) Nutritional History

- Breast: Frequency & adequacy
- Artificial or animal: Type, dilution, adequacy
- Weaning: Introduction of foods other than milk

## H) Vaccination History

- All vaccines were given according to the schedule

## I) Family History

- Positive consanguinity: Do not say -ve consanguinity
- Similar conditions
- Maternal age
- Family Pedigree

### Motor development:

- Head turn from side to side: 1 m
- Head support: 3 m
- Sitting with support: 5-6 m
- Sitting without support: 7 m
- Crawling: 9 m
- Standing: 10 m
- Walking (furniture): 12 m
- Walking (alone): 15 m

### Mental development:

- Follows objects or light: 1 m
- Social smile: 2 m
- Laugh: 4 m
- Recognition of mother: 4-6 m
- Mama & Dada: 9 m
- Waving bye-bye: 12 m

# General Examination

## A) General Look

- Fully conscious
- Alert
- Oriented (Time, Persons & Place)
- Average intelligence & Cooperative

## B) Anthropometric Measurements

- Height/Length: 2-3 yrs
- Weight
- Head circumference

## C) Vital Signs

- Heart Rate:
- Blood Pressure: Cuff??
- Respiratory Rate
- Temperature

Comment on the Pulse??

### Pulse:

90/min, regular, average volume,  
No special characters, equal on both  
sides with intact peripheral pulses

## D) Head Examination

- Pallor (Lips), Jaundice (Sclera), Cyanosis (Tongue & lips)
- Eye, Ears, Nose
- Oral cavity: Teething, CL ± P
- Fontanel

### Carotids:

- Volume: Average/Corrigan
- Thrill: AR, AS

## E) Neck Examination

- Trachea: Central
- Thyroid
- LN: Submental, submandibular, Cervical (Upper & lower)
- Arterial (Carotids)
- Venous pulsations

### Neck Veins:

- Congested or not? Level?
- Pulsating or not??

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## F) Limb Examination

- UL: Clubbing + Infective endocarditis
- LL: Clubbing + Edema (Pitting, Level)

### Limb examination in IE

- Clubbing
- Splinter hge
- Osler's nodules
- Janeway lesions
- Pulse

## G) Abdominal Examination

- Normal abdominal contour
- No organomegaly
- No ascites

## H) Chest Examination

- Normal Chest inspection & palpation
- Bilateral good equal air entry
- Normal vesicular breathing
- No adventitious sounds

### Grades of clubbing

- 1<sup>st</sup> degree: Obliteration
- 2<sup>nd</sup> degree: Parrot peak
- 3<sup>rd</sup> degree: Drum stick

## I) Cardiac Examination

- Apex
- Normal S1 & S2
- murmurs

## Vital Signs

	Heart Rate	Respiratory Rate	Blood Pressure
Newborn	130	60	80 / 60
6 months	120	50	80 / 60
1 year	120	40	80 / 60
4 years	100	25	80 / 60
10 years	90	20	100 / 65

### **Peripheral Signs of AR:** [By general examination]

- Corrigan sign: Prominent aortic pulsations
- Head nodding
- Systolic thrill over the carotids
- Big pulse volume
- Water-hammer pulse
- BP: Big pulse pressure
- Prominent capillary pulsations
- Pistol shot: Over the femoral artery (Loud sound heard by the cone)
- Duroziez sign: Systolic & diastolic bruit over the femoral artery (Bell)
- Hill's sign: BP in the LL > UL (by > 50 mmHg)

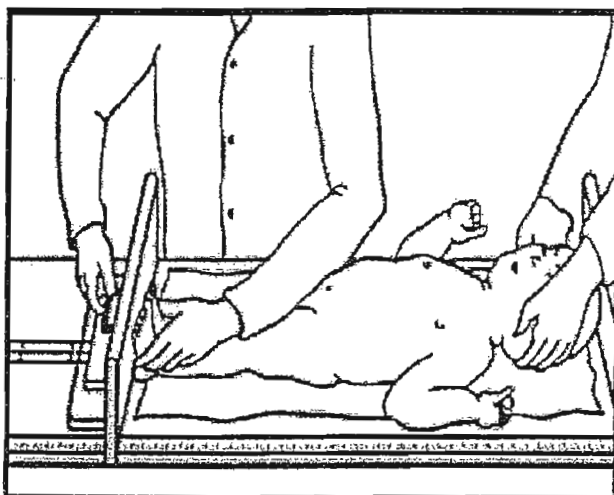
## Anthropometric Measurements

### **Supine length:**

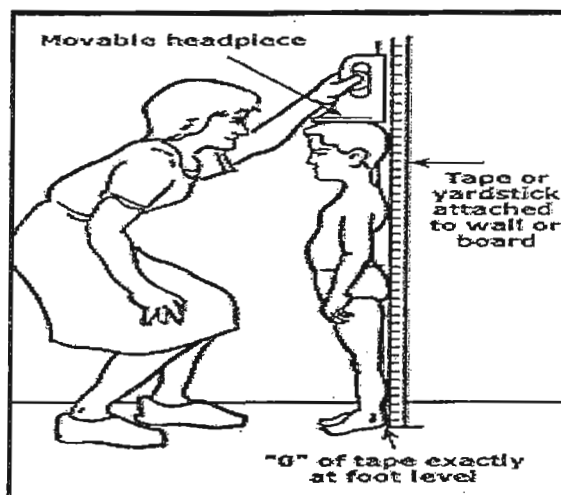
The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard

### **Standing height:**

Measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane"



Infantometer



Stadiometer



Weight

Age	Weight	Comment
Birth	3	
1 month	3.750	1 <sup>st</sup> 4 months 750 g/month
2 months	4.500	
3 months	5.250	
4 months	6	
5 months	6.500	2 <sup>nd</sup> 4 months 500 g/month
6 months	7	
7 months	7.500	
8 months	8	
9 months	8.250	3 <sup>rd</sup> 4 months 250 g/month
10 months	8.500	
11 months	8.750	
12 months	9	
2 years	12	Wt = (2 x age) +8
3 years	14	
4 years	16	
5 years	18	
6 years	20	
7 years	22.5	2.5 Kg/yr
8 years	25	
9 years	27.5	
10 years	30	

**Weight**

- Doubled at 4 months
- Tripled at 12 months
- 8 Kg at 8 months

Height & Length

Age	Height	Comment
Birth	50	
6 month	68	
1 years	75	
2 years	87	
3 years	94	
4 years	100	4-8 years 7 cm/year
5 years	107	
6 years	114	
7 years	121	
8 years	128	9-12 years- 5 cm/year
9 years	135	
10 years	140	
11 years	145	
12 years	150	

**Height Vs Length**

- Height: Standing, > 2-3 yrs
- Length: Supine, < 2-3 yrs

**Height**

- Doubled at 4 years
- Tripled at 12 years
- 75 cm at 1 year

Head circumference

Age	H. Circ.	Comment
Birth	35	12 cm in the 1 <sup>st</sup> year
6 months	43	
1 year	47	
2 years	49	6 cm in the next 11 years
6 years	51	
12 years	53	

**Head Circumference (Thin plastic tape)**

- Anteriorly: Midway between the hairline & eyebrows
- Posteriorly: Occipital prominence

Fontanel

Age	Anterior	Posterior
Birth	3 fingers	Closed
6 months	2 fingers	?? Congenital Hypothyroidism
1 year	1 fingers	
1.5 years	Closed	

# Cardiac History

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## 1. Pulmonary Congestion

- Cough
- Dyspnea, Orthopnea
- Hemoptysis
- Recurrent chest infections

### Cough:

- O, C, D
- Dry or Productive
- Relation to exercises
- Precipitating & relieving...

## 2. Systemic Congestion

- LL swelling
- Abdominal distension
- Rt hypochondrial pain
- GIT congestion: Dyspepsia

### Expectoration:

- Amount
- Color
- Relation to position
- Precipitating & relieving...

## 3. Low CO symptoms

- Syncope
- Fatigue, claudication
- Oliguria
- Pallor

### Dyspnea:

- At rest or exertion
- Orthopnea
- PND: Not common
- Precipitating & relieving...

## 4. Pain

## 5. Palpitation

## 6. Cyanosis

- Onset (Immediate or delayed)
- Hypercyanotic spells
- Squatting

## 7. Hypertension

- Headache
- Blurring of vision
- Epistaxis

## 8. Embolic symptoms

- Hemiplegia
- Blindness

## 9. Fever

- Rheumatic activity (??Criteria of rheumatic fever)
- Infective endocarditis

## 10. Manifestations of HF in infants

- Feeding difficulties, aspiration, FTT
- Sweating

### Past History:

- Recurrent tonsillitis
- Previous rheumatic fever
- Long-acting penicillin

# Cardiac Examination

## Combined Inspection & Palpation

1. **Precordial bulge:** RV hypertrophy
2. **Scars:** Median sternotomy (Open heart) or Lateral thoracotomy (PDA closure)
3. **Dilated veins**
4. **Apex:** It is the outermost lowermost seen &/or felt impulse  
 Normally in the 5<sup>th</sup> space just inside MCL  
 4<sup>th</sup> space just outside MCL in children < 4 yrs
  - **Site:** Shifted outwards (RVE) or out & downwards (LVE)
  - **Extent:** Localized (LVE) or Diffuse (RVE)
  - **Timing:** Systolic bulge (LVE) or systolic retraction (RVE)
  - **Character:** Hyperdynamic, sustained or slapping
  - **Palpable sounds:** 1<sup>st</sup> heart sound (MS)
  - **Thrill:** Systolic (MR) or diastolic (MS)
5. **Epigastric pulsation:** Origin??
  - **Tips of the fingers:** RVE
  - **Palmar aspect:** Aortic pulsation
6. **Lt Parasternal pulsation:** RVE  
 Thrill: VSD
7. **Pulmonary area:** Pulmonary hypertension  
 Palpable 2<sup>nd</sup> sound (= Diastolic shock) in pulmonary HTN
8. **Aortic area:** Systemic hypertension

### Timing:

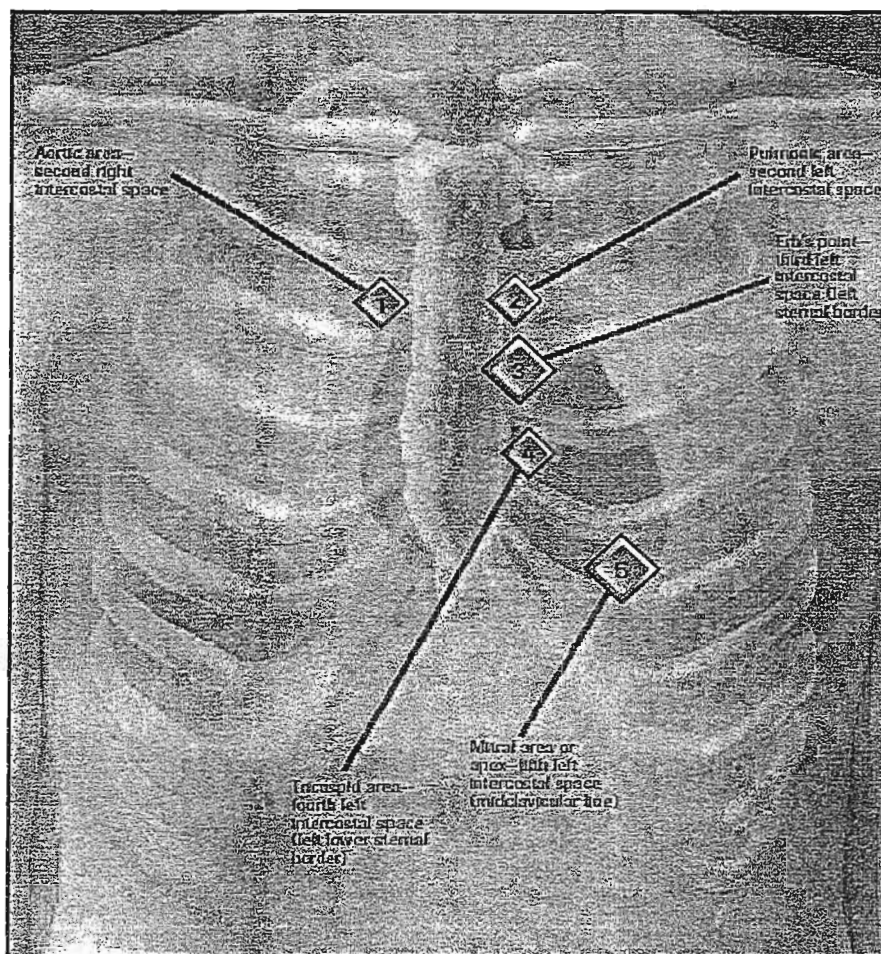
- Carotid artery
- Radial artery

RVE	LVE	Pulmonary HTN

## Inspection & Palpation

- There is no precordial bulge
- The apex is in the 6<sup>th</sup> Lt intercostal space outside MCL, localized, systolic bulge, hyperdynamic, no palpable sound, no palpable thrill
- There is Lt parasternal pulsation
- There is epigastric pulsation of RV origin (Tips of fingers)
- There is pulmonary pulsation & palpable 2<sup>nd</sup> sound (Diastolic shock)
- No aortic pulsation

## Auscultation



### A) Comment on Heart Sounds

1. First sound: [= Closure of mitral & tricuspid valves]  
Over the mitral & tricuspid areas
2. Second sound: [= Closure of aortic & pulmonary valves]  
Over the mitral & tricuspid areas

#### 1<sup>st</sup> Sound:

- Muffled in MR
- Accentuated in MS

#### 2<sup>nd</sup> Sound:

- Accentuated in Pulm. HTN over the pulmonary area

### B) Comment on Murmurs

Murmur	Character	Timing	Max. intensity	Selective propagation
MS	Rumbling	Middiastolic-Presystolic	Apex	Localized
MR	Soft/Harsh	Pansystolic	Apex	Axilla
AS	Harsh	Ejection systolic	A1	Carotids & Apex
AR	Soft	Early diastolic	A2	Apex
PS	Harsh	Ejection systolic	Pulmonary area	Lt Infra-clavicular area
VSD	Harsh	Pansystolic	Lt parasternal	All over precordium
PDA	Machinery	Continuous (S & D)	Lt Infra-clavicular	Pulmonary area

#### Grades of the murmur:

1 2 3: No Thrill

4 5 6: Thrill

MR + ↑↑ S1 = Double mitral

## **Diagnosis of a cardiac case**

- 1. Etiological**
- 2. Anatomical**
- 3. Functional**
- 4. Complications**

## **Investigations of a cardiac case**

- 1. Laboratory**
- 2. Imaging**
- 3. Invasive**

## **Differential Diagnosis of a cardiac case**

# **Congenital Heart Disease**

## **Classification of CHD**

### **A) Congenital Cyanotic HD (20%)**

#### **Causes (Individual lesions)**

<b>↓↓ Pulmonary Blood Flow</b>	<b>↑↑ Pulmonary Blood Flow</b>
<b>A) RVH</b> <ul style="list-style-type: none"> <li>Fallot tetralogy</li> <li>TGA with PS</li> <li>DORV with PS</li> <li>PS with VSD</li> <li>Pulmonary atresia with VSD</li> </ul>	<b>A) RVH</b> <ul style="list-style-type: none"> <li>TGA</li> <li>TAPVR</li> <li>HLHS</li> </ul>
<b>B) LVH</b> <ul style="list-style-type: none"> <li>Tricuspid atresia</li> <li>Pulmonary atresia</li> </ul>	<b>B) LVH, RVH or both</b> <ul style="list-style-type: none"> <li>Single ventricle</li> <li>Truncus arteriosus</li> </ul>
<b>C) RA Enlargement</b> <ul style="list-style-type: none"> <li>Ebstein anomaly</li> </ul>	<b>C) Eisenmenger syndrome</b>

#### **Onset of Cyanosis**

<b>Early onset</b>	<b>Delayed onset (1-2 m)</b>	<b>Variable onset</b>
<ul style="list-style-type: none"> <li>TGA</li> <li>TAPVR</li> <li>HLHS</li> <li>Tricuspid atresia</li> <li>Pulmonary atresia</li> </ul>	<ul style="list-style-type: none"> <li>Fallot tetralogy</li> <li>TGA with PS</li> <li>DORV with PS</li> <li>PS with VSD</li> <li>Pulmonary atresia with VSD</li> </ul>	<ul style="list-style-type: none"> <li>Ebstein anomaly</li> <li>Single ventricle</li> <li>Truncus arteriosus</li> </ul>

#### **Features**

	<b>↓↓ PBF</b>	<b>↑↑ PBF</b>
<b>A) History</b> <ul style="list-style-type: none"> <li>Recurrent chest infection</li> <li>Squatting</li> <li>HF</li> </ul>		
<b>B) Examination</b> <ul style="list-style-type: none"> <li>Precordium</li> <li>S2</li> <li>HF</li> </ul>		
<b>C) Investigation</b>		

#### **Diagnosis (Examples)**

- ☒ Congenital cyanotic heart diseases with ↓↓ PBF, most probably Fallot tetralogy, Why?
- ☒ Congenital cyanotic heart diseases with ↑↑ PBF, most probably TGA, Why?

- PBF
- Onset of cyanosis
- Ventricular enlargement

Complicated with chest infections, HF, stroke...

## B) Congenital Acyanotic HD (80%)

### Causes (Individual lesions)

↑↑ Pulmonary Blood Flow	Normal Pulmonary Blood Flow
A) RVH ▪ ASD (Ostium secundum & primum)	A) RVH ▪ PS
B) LVH ▪ PDA	B) LVH ▪ AS ▪ Coractation
C) RVH & LVH ▪ VSD ▪ ECD	

### Diagnosis

Congenital acyanotic heart diseases with ↑↑ PBF, Biventricular hypertrophy, most probably VSD, Complicated with chest infections, HF..., Why?

- PBF
- Ventricular enlargement
- Murmur & Thrill

### Diagnosis

Congenital acyanotic heart diseases with ↑↑ PBF, Lt ventricular hypertrophy, most probably PDA, Complicated with chest infections, HF..., Why?

- PBF
- Ventricular enlargement
- Murmur & Hyperdynamic circulation

#### **Hyperdynamic Circulation:**

- HR: Tachycardia
- Big pulse volume
- Water-hammer pulse
- BP: Big pulse pressure?
- Prominent carotid pulses

### Examination of a case of CHD is NOT completed except after

1.
  - a.
  - b.
- 2.

### CHD in the Exam

1. Fallot
2. TGA
3. VSD, PDA (How to differentiate??)
4. Others: COA, PS, AS

### Cardiac cases in the Exam

1. RHD
2. CHD
3. Cardiomyopathy
4. Cardiac + Neuro-
5. Cardiac + Chest

## Important remarks

1. Prophylaxis against **infective endocarditis** is indicated in all patients with CHD except...
2. ASD is associated with **wide fixed splitting** of S2 & ejection systolic murmur (Why??)
3. BP should be measured in UL & LL
4. **Left axis deviation** in neonates indicates tricuspid atresia
5. Fallot tetralogy is **not** associated with HF nor chest infections
6. **Hemiplegia** in Fallot may be due  $\Rightarrow$
7. PDA murmur is **machinery** (Systolic & diastolic) & So...
8. Ebstein anomaly = **arrhythmias**
9. HLHS = Neonatal collapse
10. Duct-dependent CHD

### Hemiplegia in Fallot:

- Thrombosis
- Brain abscess
- Infective endocarditis

## Cardiac Murmurs

Murmur	Character	Timing	Max. intensity	Selective propagation
MS	Rumbling	Middiastolic-Presystolic	Apex	Localized
MR	Soft/Harsh	Pansystolic	Apex	Axilla
AS	Harsh	Ejection systolic	A1	Carotids & Apex
AR	Soft	Early diastolic	A2	Apex
PS	Harsh	Ejection systolic	Pulmonary area	Lt Infra-clavicular area
VSD	Harsh	Pansystolic	Lt parasternal	All over precordium
PDA	Machinery	Continuous (S & D)	Lt Infra-clavicular	Pulmonary area
CoA	Harsh	Ejection systolic	Lt parasternal	Inter-scapular

## Myocarditis & Cardiomyopathy

- History: Preceding viral infection, Acute onset, HF symptoms
- Examination: Cardiomegaly, MR, TR, arrhythmias
- Investigation: CPH-MB, LDH, AST, ECG

## Antibiotic prophylaxis

### 1. Oral, Respiratory & Esophageal

	Agent	Regimen	
		Dose	When?
Most patients	Oral Amoxicillin	Single dose 50 mg/Kg	1 hour before procedure
Unable to take PO	IM/IV Ampicillin	Single dose 50 mg/Kg	30 min before procedure
Allergy to penicillin	Oral Azithromycin	Single dose 15 mg/Kg	1 hour before procedure
	Oral Cephalexin	Single dose 50 mg/Kg	1 hour before procedure
	Oral Clindamycin	Single dose 20 mg/Kg	1 hour before procedure

### 2. GU & Non-esophageal GIT

	Agent	Regimen	
		Dose	When?
High-risk patients Before & After	IM/IV Ampicillin & IM/IV Gentamicin	50 mg/Kg/dose + 1.5 mg/Kg/dose	30 min before procedure
	IM/IV Ampicillin or Oral Amoxicillin	25 mg/Kg/dose	6 hour after procedure
High-risk patients & Allergy to penicillin	IV Vancomycin & IM/IV Gentamicin	20 mg/Kg (over 1-2 hr) + 1.5 mg/Kg/dose	30 min before procedure



# Abdominal Sheet

## History

### A) Hematological Symptoms

- RBCs: Pallor, Blood transfusion...
- Platelets: Purpura, bleeding, masses
- WBCs: Abdominal masses, bony pains, arthritis

### B) Hepatic Symptoms

- Jaundice
- Color of urine & stools
- Manifestation of LCF
- Manifestation of Portal HTN: Bleeding, Masses??
- Abdominal distension & masses

### C) Urinary Symptoms

- Dysuria, Frequency, Urgency, Incontinence
- Oliguria, Polyuria
- CRF: Edema, FT, HTN, Dialysis

### D) GIT

- Upper: Vomiting, Dysphagia, Hematemesis, Melena
- Lower: Diarrhea, Constipation, Bleeding/rectum

### E) Pain

- O, C, D
- Site, radiation
- Association
- Precipitating & relieving...

#### Blood transfusion:

1. Onset
2. Frequency (Initial, Course)
3. Splenectomy ( $\Delta$  Frequency)
4. Complications
5. Iron chelation

#### Bleeding:

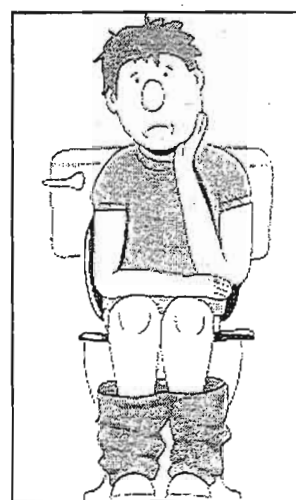
1. Epistaxis
2. Bleeding gums
3. Hemoptysis
4. Hematemesis
5. Hematuria
6. Melena
7. Bleeding/Rectum
8. Puncture sites
9. Circumcision
10. DCL

**Melena:** Dark, altered blood due to bleeding above D/J junction

**Splenomegaly** is the most important diagnostic sign of portal hypertension

#### Manifestation of LCF:

1. General Failure of health Anorexia, easy fatigability
2. Fever (Bacteremia)
3. Feter hepaticus (Mousy odor)
4. Jaundice
5. Ascites & edema
6. Hepatic encephalopathy
7. Endocrinal Gynecomastia, Amenorrhea
8. Cutaneous: White nail, Parotid enlargement, Palmar erythema, Spider nevi
9. CVS manifestations: Hyperdynamic circulation
10. Hematological: Anemia, Pancytopenia, Bleeding
11. Hepatorenal: Oliguria
12. Infection: Spontaneous bacterial peritonitis
13. Metabolic: Hypoglycemia or hyperglycemia
14. Picture of the cause: Varices in cirrhosis



# Abdominal Examination

## A) Inspection

1. Abdominal Contour
2. Respiratory movements
3. Midline
  - Subcostal angle: Wide in upper abdominal masses
  - Divarication of rectiEpigastric pulsation: Origin?
  - Umbilicus: Site, Shape, Discharge, Impulse on cough
  - Pubic hair... Why?
  - External genitalia
  - Hernial orifices
4. Others
  - Scars: Site, Length, Healing
  - Dilated veins (DD: Visible veins)
5. Back
  - Deformities: Pott's disease, Kyphosis, Scoliosis
  - Scars: Meningomyelocele

## B) Palpation

1. Superficial Palpation: No tenderness, No rigidity, No superficial masses
2. Deep Palpation:
  - Liver: Hepatomegaly, 10 cm below costal margin in the Rt MCL, 6 cm below X/S junction in the midline, rounded border, smooth surface, firm in consistency, not tender with the upper border in the 5<sup>th</sup> IC space ( $\pm$  Span)
  - Spleen: Splenomegaly, 10 cm below costal margin along its longitudinal axis, rounded border, smooth surface, firm in consistency, not tender with the notch is felt along its anterior border
  - Kidneys:
  - Masses: Wilms, Neuroblastoma

## C) Percussion

- Confirmation of organomegaly: Liver, Spleen
- Detection of Ascites:
  - Marked: Transmitted thrill
  - Moderate: Bilateral shifting dullness
  - Mild: Knee-chest position

## D) Auscultation

- Intestinal sounds: Intestinal obstruction, Ileus
- Venous hum: Portal HTN (Midway between X/S & Umbilicus)
- Arterial bruit: Renal artery stenosis (Renal angle)

## Stages of Puberty (Tanner staging)

### ☒ Females:

	Pubic Hair	Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

### ☒ Males:

	Pubic Hair	Penis	Testes (orchidometer)
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Scanty, lightly pigmented	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth )	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

# Chronic Hemolytic Anemia

## Thalassemia Sheet

### History

- Main symptoms: Pallor, jaundice, Abdominal masses
- Onset of symptoms
- Onset blood transfusion
- Frequency of blood transfusion
- Complications of blood transfusion
- Change of pattern?
- Splenectomy
- Crises: All except
- Vaccination...
- Family history

### Examination

- a. **Vital signs:** Hyperdynamic circulation (↑↑HR, big pulse volume, ↑↑ heart sounds...)
- b. **Anthropometric measurements**
  - Height: Short stature
  - Skull circumference: ↑↑ "Macrocephaly"
- c. **Head & Neck**
  - Pallor (May be absent?)
  - Jaundice
  - Mongoloid facies: Large head, depressed nasal bridge, prominent maxillae, protruding central incisors
- d. **Cardiac**
  - Heart sounds: ↑↑
  - Hemic murmur
- e. **Abdominal**
  - HSM
  - Scar of splenectomy??
  - Other scars

### Diagnosis

A case of chronic hemolytic anemia, most probably thalassemia major

### Iron chelating therapy (When Serum ferritin > 1000 ng/ml, usually > 4-5 years)

#### 1. Deferoxamine (Desferal)

Dose: 40-60 mg/Kg/day electronic SC pump over 10-12 hrs/day for 5-6 days/wk.

IV Deferoxamine may be used in severe cases

Side effects:

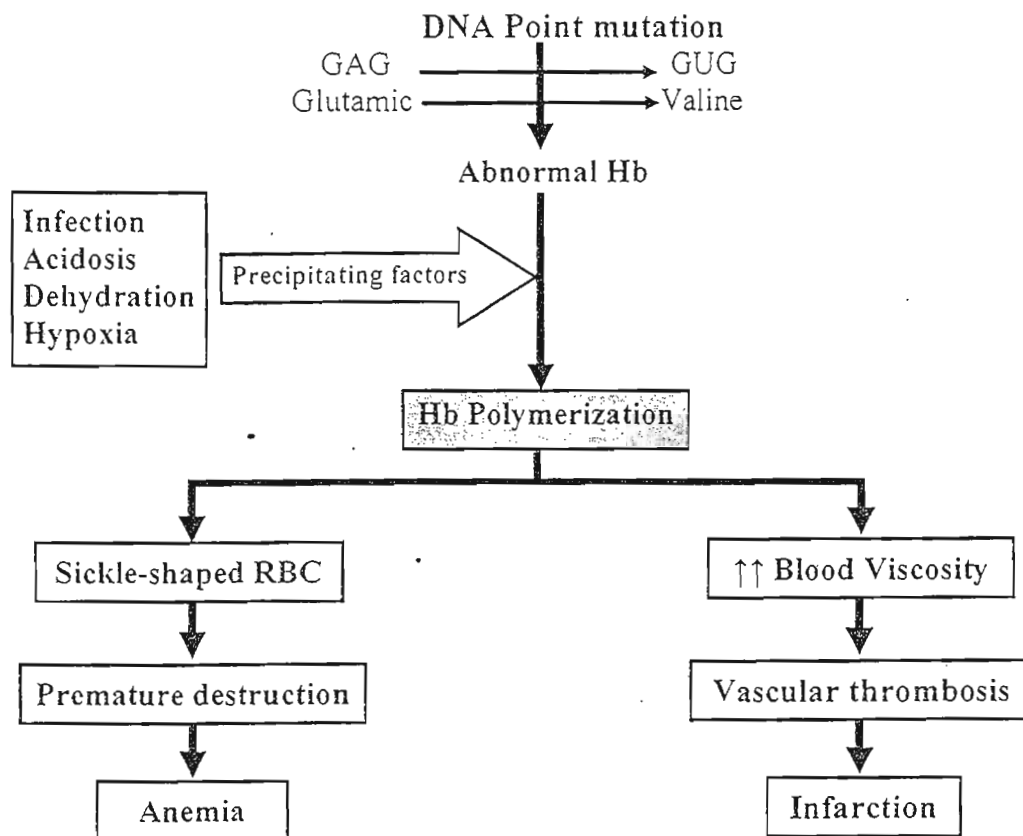
- Ototoxicity & ↓↓ Visual field & acuity
- Local: pruritis, swelling & rash

#### 2. Deferiprone (L-1): Oral chelating agent

Side effects: Neutropenia, arthralgia, arthritis

#### 3. ICL 670: Oral chelating agent

## Sickle Anemia Sheet



### History

- Main symptoms: Pains, Pallor, Jaundice, VOC
- Chest pain, stroke, priapism, renal
- Hand/foot swelling, Arthritis
- Infection
- Gall stones
- Exchange transfusion
- Blood transfusion
- Vaccination
- Family history

### Examination

- As before +
- Neurological

### Diagnosis

A case of chronic hemolytic anemia, most probably Sickle cell anemia

### Indications of blood transfusion/ exchange transfusion:

1. Anemia
2. Refractory painful crisis
3. Splenic sequestration
4. Stroke (overt, silent, TCD > 200)
5. Acute chest S
6. Elective surgery (anesthesia)
7. Priapism
8. Pregnancy (latter part)

### Aim:

To ↓↓ HbS < 30 %

## Sickle & ...

## Sickle Thalassemia

- 1.
- 2.

## Thalassemia Intermedia

General features of thalassemia, but...

- Onset: after 2 years of age
- Hb level: maintained between 6-8 g %
- Do not require regular blood transfusion

3

## Hereditary Spherocytosis

	Thalassemia major	Sickle cell anemia	H. Spherocytosis
Onset			
Inheritance			
Common in			
Diagnosis			
Main Rx			

### Treatment



#### Splenectomy:

1. Clinical cure (anemia & jaundice)
2. Biochemical & morphological
3. Spherocytes & osmotic fragility

## Autoimmune Hemolytic Anemia

- Acute onset of pallor, jaundice & dark-colored urine (Hemoglobinuria)
- Marked splenomegaly
- May be 1ry or 2ry (SLE)

## G-6-PD Deficiency

- Acute onset of pallor, jaundice & dark-colored urine (Hemoglobinuria)
- Follows exposure to oxidant stress
- Enzyme assay, When?
- XL-R

## Aplastic anemia

## Fanconi anemia

- Short stature
- Microcephaly, Microphthalmia
- Skin pigmentation (café-au-lait patches)
- Mental retardation & hyperreflexia
- Thumb anomalies (Triphalangeal or hypoplastic)
- Radius anomalies
- Renal anomalies (ectopic, dysplasia or horseshoe)
- Pancytopenia (mean age = 6-8 yrs)
- ↑↑ Risk of malignancy (leukemia)

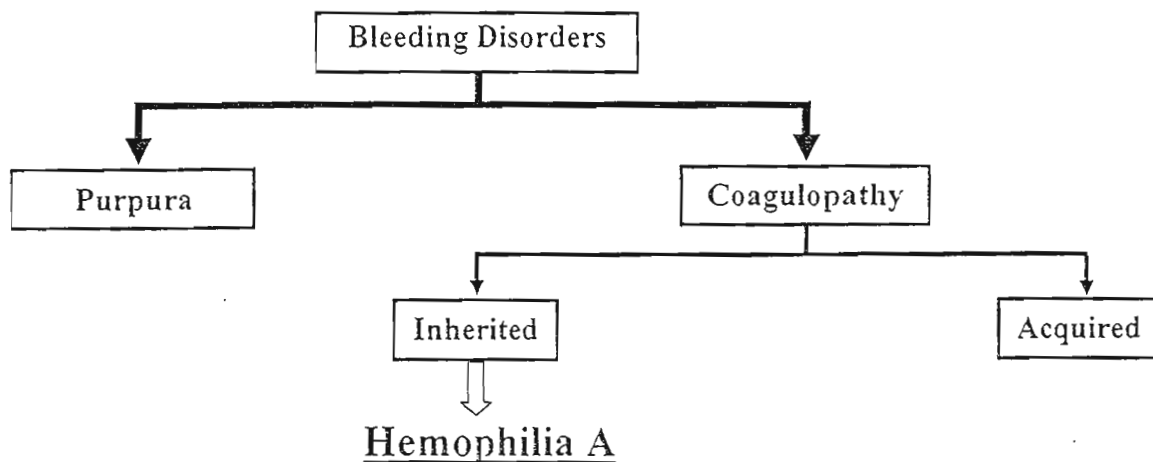
#### DD of café-au-lait spots:

1. Neurofibromatosis
2. Fanconi anemia
3. McCune Albright \$
4. Chediak-Higashi \$
5. Ataxia telangiectasia
6. Bloom \$
7. Tuberous sclerosis

# Coagulation Disorders

## Bleeding

### Classification



## Hemophilia A

- Bleeding tendency
- 1<sup>st</sup> trauma...
- Joint...
- Family history, Who??
- XL-R
- PT Vs PTT

	Purpura	Coagulation disorders
	ITP	Hemophilia
Defect	Platelet or vessel wall	Coagulation factors
Skin lesions	Petechiae 1-2 mm Ecchymosis 1-2 cm	Ecchymosis
Site of bleeding	Mucous membranes (mouth, gums, epistaxis, conjunctiva) Internal Hge (ICH) less common	Deep bleeding; joints (hemoarthrosis), muscle (hematoma)
Relation to trauma	Immediate Usually spontaneous	Usually delayed (oozing) Usually traumatic

## Vitamin K Deficiency

- 1.
- 2.

# Immune Thrombocytopenic Purpura Sheet

## History

### Personal History

- Age: 1-4 years

### Complaint

- Reddish spots all over the body
- Mucous membrane bleeding

### Present History

- Analysis of the **complaint** (Onset, Course, Duration)
  - Preceding upper respiratory infection
  - Site
  - Color: Initially red then change with time
- Ask about **other bleeding sites**
  - See box
- Is it ITP, Leukemia or Aplastic anemia?
  - Fever
  - Organomegaly & Lymphadenopathy (Body masses)
  - Arthralgia
  - Blood transfusion
- **Drugs**
- **Investigations & Treatment of ITP**
  - BM aspirate
  - Steroids: IV pulse steroid therapy is the main line of Rx
- **Manifestations of Collagen-vascular diseases**
  - Arthritis, malar rash, edema,

#### Bleeding:

1. Epistaxis
2. Bleeding gums
3. Hemoptysis
4. Hematemesis
5. Hematuria
6. Melena
7. Bleeding/Rectum
8. Puncture sites
9. Circumcision
10. Coma & convulsions

Other Items of History Vaccination, Perinatal, Developmental, Past, Family, Nutritional

### Differential Diagnosis of ITP

	ITP	Aplastic anemia	Leukemia
Fever	No	Present	Present
Bleeding	Present	Present	Present
Pallor	Absent (except...)	Present	Present
General Examination	Good	Bad	Bad
HSM	Absent	Absent	Present
LN	Absent	Absent	Present
CBC	Thrombocytopenia	Pancytopenia	Anemia, thrombocytopenia, WBC: Normal, ↑↑ or ↓↓
Investigations	BM aspirate	BM aspirate & biopsy	BM aspirate
Treatment	Steroids	BM transplantation	Chemotherapy



# Examination

## General Look

### Anthropometric measurement

- Weight
- Length/Height
- Skull circumference

### Vital Signs

- Heart rate
- Temperature: Fever in aplastic & leukemia (infection)

### Head & Neck Examination

- Pallor: When??
- Subconjunctival hemorrhage
- LN

### Abdominal Examination

- No organomegaly

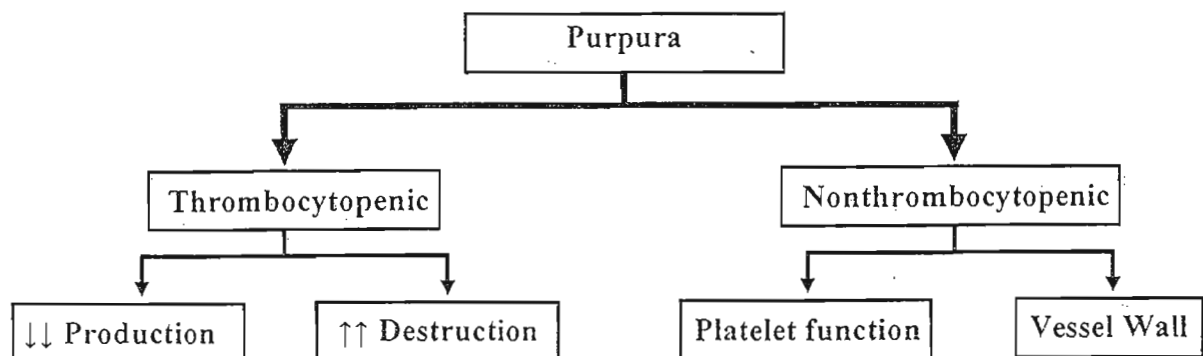
### Limb & Trunk Examination

- Purpura: Petichiae & ecchymoses
  - Site
  - Nature: Do not blanch on pressure
  - Color: Initially red then change with time
- Bone tenderness: Leukemia

## Purpura

4

### Classification



## Henoch-Schonlein Purpura

1. Skin (100%): Purpuric eruption mostly on the LL & buttocks, sparing the trunk & UL
2. Arthritis (70%): Large joints (knees & ankles), Transient with spontaneous resolution
3. GIT (50%): Abdominal pain, bleeding (hematemesis & bleeding per rectum)
4. Nephritis (30%): Hematuria, proteinuria, NS, GN

4

# Portal Hypertension

## Presentation



## History

- Main symptoms: Bleeding??
- Perinatal history: Admission to NICU, Neonatal jaundice, exchange transfusion
- Manifestations of LCF
- Cardiac symptoms

## Examination

- Splenomegaly: Most important sign of portal hypertension
- Hepatomegaly: Absent (prehepatic), shrunken (Cirrhosis), marked (Posthepatic)
- Ascites: especially in cirrhosis

# Abdominal Masses

## Neuroblastoma & Wilms

	Neuroblastoma	Wilms tumor
Age	< 3 yrs	Around the age of 3 yrs
Site	Rt or Lt upper quadrants	Rt or Lt upper quadrants
Consistency	Hard	Firm
Surface	Irregular or nodular	Smooth
Midline**	Commonly crosses the midline	Does Not cross the midline
Associations	HSM, Proptosis, SC nodules, anemia, bony pains	Hematuria
Diagnosis	US & CT abdomen, BM study	US & CT abdomen, Biopsy
Prognosis	Worse	Better

## Intestinal Lymphoma

## Polycystic Kidneys

- Term
- Side
- Antenatal
- Presentation
- Association
- Example

Others Ovarian, Mesenteric, Omental, Pancreatic

## Ascites

### Etiology

- A) Portal HTN
- B) Hypoalbuminemia
  - a. Liver cell failure
  - b. Nephrotic syndrome
  - c. Malabsorption (Protein-losing enteropathy)
- C) Peritoneal diseases
  - a. Peritonitis: Bacterial, TB
  - b. Malignancy: Lymphoma, Neuroblastoma
- D) Chylous
  - a. Congenital lymphatic malformation
  - b. Thoracic duct injury (Trauma or surgery)
  - c. Lymphatic obstruction (LN, masses, bands)
- E) Urinary ascites
- F) Biliary ascites

#### Causes of G. abd. distension:

- Acites
- Gaseous (IO)
- Tumors
- UB distension
- Fecal retention
- Pregnancy
- Obesity

#### Diagnosis of chylous ascites depends on:

- Paracentesis after fat-containing meal
- Ascitic fluid: ↑↑ TAG, Lymphocytes & Ptn

## Generalized LN Enlargement

1. Infections
  - a. Bacterial: Typhoid, TB, Brucellosis, sepsis
  - b. Viral: EBV (infectious mononucleosis), CMV, Viral hepatitis, VZ
  - c. Protozoa: Malaria, Leishmaniasis
  - d. Fungal: Histoplasmosis
  - e. Rickettsial: Rocky Mountain spotted fever
2. Neoplastic
  - a. Hematologic: Leukemia, lymphoma (Hodgkin & non-Hodgkin)
  - b. Non-hematologic: Neuroblastoma
3. Immune
  - a. Collagen-vascular diseases: Systemic onset JRA & SLE
  - b. Immunodeficiency: Chronic granulomatous disease & Chediak-Higashi disease
4. Storage diseases
  - a. Gaucher
  - b. Neimann-Pick
5. Drug: Phenytoin
6. Miscellaneous: Sarcoidosis, Hyperthyroidism (Graves Disease)

## Cervical LN Enlargement

1. Infection
  - a. Bacterial: Pharyngitis & tonsillitis
  - b. Viral: URT infection, EBV (infectious mononucleosis), CMV, VZ
  - c. Mycobacteria: TB & atypical mycobacteria (M. avium, intracellulare, kansasii, marinum)
  - d. Fungal: Histoplasmosis
  - e. Protozoa: Toxoplasmosis
  - f. Cat scratch disease (Bartonella henselae), Tularemia (Francisella tularensis)
2. Neoplastic: Lymphoma, leukemia
3. Immune: Kawasaki disease
4. Occipital LN: Pediculosis, Rubella, scalp & ear infection

## Stages of Puberty (Tanner staging)

### ☒ Females:

	<b>Pubic Hair</b>	<b>Breasts</b>
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

### ☒ Males:

	<b>Pubic Hair</b>	<b>Penis</b>	<b>Testes (orchidometer)</b>
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Scanty, lightly pigmented	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth )	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

## Metabolic HSM

1. Galactosemia (& Hereditary fructose intolerance)
2. Tyrosinemia
3. Glycogen storage diseases
4. Gaucher
5. Niemann-Pick
6. Wilson
7. Cystic fibrosis
8.  $\alpha$ -1-Antitrypsin deficiency
9. Hemochromatosis
10. Gangliosidosis (GM1, GM2), MPS (Hurler)

## Galactosemia

### Etiology

1. Galactose 1-P-uridyltransferase deficiency\*\* (Classic Galactosemia)
2. Galactokinase deficiency (Only cataract)
3. Epimerase deficiency

### Clinical Picture

- Jaundice (Cholestasis)
- Hepatomegaly, splenomegaly, ascites
- Hypoglycemia, convulsions, lethargy
- FTT, vomiting
- Cataract
- E.coli sepsis

### Diagnosis

- Reducing substances in urine (When?)
- Enzyme assay

### Treatment

## Hereditary fructose intolerance

## $\alpha$ -1-Antitrypsin deficiency

- ☒ **Hepatic:** Cholestasis, Cirrhosis, Hepatomegaly, Cirrhosis
- ☒ **Chest:** Asthma, wheezes, recurrent chest infections, emphysema (30-40 yrs)

# Glycogen Storage Diseases

## Types

Disease	Enzyme Defect	Clinical Picture
Type Ia (Von Gierke)	G-6-Phosphatase	Doll face Marked Hepatomegaly Fasting hypoglycemia (Seizures) Hypercholesterolemia Lactic acidosis ↑↑ Uric acid
Type Ib	G-6-Phosphate Translocase	GSDI + Neutropenia
Type II (Pompe)	Acid maltase	Hepatomegaly Myopathy Cardiomyopathy
Type III (Cori)	Debranching	Hepatomegaly Hypoglycemia Myopathy
Type IV (Andersen)	Brancher	HSM Liver cirrhosis LCF Ascites
Type V (Mc Ardle)	Muscle Phosphorylase	Exercise intolerance Muscle cramps Easy fatigability
Type VI (Hers)	Liver Phosphorylase	
Type VII (Tauri)	PFK	V + Hemolytic anemia
Type VIII		??Ataxia
Type IX	Phosphoglycerate Kinase	
Type X		
Type XI (Fanconi-Bickel)	Glucose Transporter II	FTT + Fanconi + Hepatomegaly
Type 0	Glycogen synthase	Fasting hypoglycemia (Seizures) Prolonged hyperglycemia (after meals)

## Diagnosis

- Biochemical
- Liver biopsy
- Enzyme assay (Liver)

## Treatment

- Avoid...
- Enzyme?
- Liver transplantation

Hepatic	Muscle	Mixed

## Gaucher Disease

### Etiology

Glucocerebrosidase ( $\beta$ -Glucosidase) deficiency (AR<sup>1</sup>)

### Clinical Picture

#### Gaucher Disease:

- Lysosomal storage disease
- Carrier rate in Jews = 1/18
- Enzyme therapy
- Unexplained Organomegaly

	Type 1 (99%)	Type 2	Type 3
Other Names	Adult type Non-Neuropathic	Infantile Neuropathic	Juvenile
Onset	Variable	Infancy	Early childhood > 2yrs
C/P	<ul style="list-style-type: none"> <li>▪ HSM (S &gt; L)</li> <li>▪ Anemia</li> <li>▪ Thrombocytopenia</li> <li>▪ Bony pains</li> <li>▪ Normal mentality</li> </ul>	<ul style="list-style-type: none"> <li>▪ Head retraction</li> <li>▪ Hypertonia</li> <li>▪ Laryngospasm</li> <li>▪ Stridor</li> <li>▪ Squint</li> <li>▪ Cranial nerve...</li> <li>▪ Rapid neurologic...MR</li> <li>▪ HSM</li> <li>▪ Death in the 1<sup>st</sup> 2 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Neurologic (Less severe)</li> <li>▪ MR</li> <li>▪ Ataxia</li> <li>▪ Myoclonic epilepsy</li> <li>▪ Gaze palsy</li> <li>▪ HSM</li> <li>▪ Death by age of 10-15 y</li> </ul>

### Investigations

- X-rays: Lytic lesions, Erlenmeyer flask deformity (Distal femur)
- BM examination: Gaucher cells
- Enzyme assay

### Treatment

- Enzyme replacement: Cerezyme
- BMT
- Gene therapy

## Niemann-Pick Disease

### Etiology

Sphingomyelinase deficiency

### Clinical Picture

	Type A	Type B	Type C
Other Names	Acute infantile	Non-Neuropathic	
Onset	1 <sup>st</sup> few months of life	Infancy	Early childhood > 2yrs
C/P	<ul style="list-style-type: none"> <li>▪ HSM (L &gt; S)</li> <li>▪ FTT, feeding difficulties</li> <li>▪ Neurological...MR</li> <li>▪ Cherry-red spots (50%)</li> <li>▪ Spasticity</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ Pulmonary involvement</li> <li>▪ No neurological...</li> <li>▪ Normal mentality</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Slowly progressive neurologic course</li> <li>▪ Gaze palsy</li> <li>▪ HSM</li> </ul>

### Investigations

- BM examination: Foam cells (NP cells)
- Enzyme assay (Fibroblasts)

### Treatment

Supportive

# Tyrosinemia

## Etiology

Fumarylacetate hydrolase deficiency (Type I)

## Clinical Picture

- Jaundice (Cholestasis)
- Hepatomegaly, splenomegaly, ascites
- Hypoglycemia, convulsions, lethargy
- FTT, vomiting
- Cirrhosis
- Peripheral neuropathy
- Renal: RTA (Fanconi)

## Diagnosis

- Urine succinylacetone
- $\alpha$ -fetoprotein
- LFT
- Liver enzymes
- Renal

## Treatment

- Diet
- NTBC

# Wilson Disease (Hepatolenticular Degeneration)

## Etiology

AR<sup>13</sup>

## Pathogenesis

Copper accumulation in liver, brain, kidney & cornea

Typically, Wilson disease is not clinically manifest < 5 yrs

## Clinical Picture

- Hepatic: Any form of liver disease
- Neurological: Chorea, Dystonia, Tremors & behavioral changes
- Others: RTA, Hemolytic anemia, arthritis

## Investigations

1.  $\downarrow\downarrow$  Serum ceruloplasmin "best screening test"
2.  $\uparrow\uparrow$  Urinary Copper (Before & after D-penicillamine)
3. Slit-lamp examination
4. Liver biopsy ( $\uparrow\uparrow$  Liver Copper)
5. Renal
6. Screening for presymptomatic
7. Genetic screening

Kayser-Fleischer ring is present in all patients with neurological manifestations

## Treatment

1.  $\downarrow\downarrow$  dietary Copper (Shellfish, nuts, liver)
2. Zinc acetate:  $\downarrow\downarrow$  Copper intestinal absorption
3. D-penicillamine (20 mg/Kg/day)



# Neurology History

## A) Motor system

- Weakness or paralysis
- Convulsions or abnormal movements (Tics, tremors, ...)

## B) Sensory system

- Anesthesia
- Hypersthesia or parasthesia

## C) Sphincteric

- Urine
- Stools

## D) ↑↑ ICT symptoms

- Headache
- Vomiting
- Blurring of vision

## E) Cranial nerve affection

Cranial Nerve	Symptoms
I	▪ Smell
II	▪ ↓↓ Visual acuity ▪ Visual field defect
III, IV, VI	▪ Squint ▪ Diplopia ▪ Ptosis
V	▪ Difficult mastication ▪ ↓↓ Face sensation
VII	▪ Accumulation of food behind cheek ▪ Dribbling of saliva
VIII	▪ ↓↓ Hearing ▪ Vertigo, Tinnitus
IX, X, XI, XII	▪ Dysphagia ▪ Dysarthria ▪ Nasal tone of voice (Hoarseness of voice) ▪ Nasal regurgitation

### **Weakness or Paralysis:**

- Onset, Course, Duration
- Unilateral / Bilateral...
- UL / LL
- Distal / Proximal
- Flexor / Extensor

### **Convulsions:**

- Site of onset
- Character (Tonic...)
- Precipitating factors???
- Recurrence
- Rx (Effective?)

## F) Macrocephaly

- Onset, course, duration
- Rx

## G) Other system affection??

- Cardiac: RHD ( ), CHD ( )
- Hematological: Pain & blood transfusion ( )
- Skin:
- Respiratory:

### **Important Remarks:**

- Personal history: Handedness...
- Perinatal history: Antenatal ( ), Natal ( ), Postnatal ( )
- Developmental history: Progressive deterioration...
- Nutritional history
- Family history
- Past history

# Neurological Examination

## 1. General Look

- Fully conscious, Alert, Oriented (Time, Persons & Place)
- Average intelligence & Cooperative

## 2. Speech

- Aphasia:
- Staccato:
- Monotonous:

Manifestations of Cerebellar ataxia occur on the **same** side of the lesion

## 3. Gait

- Archicerebellar lesions: Wide-base (drunken gait)
- Neocerebellar lesions: Deviation to the same side (**Unilateral**) or zigzag (**bilateral**)
- UMNL (Hemiplegia): Circumduction
- UMNL (Paraplegia): Scissoring
- Peripheral Neuropathy: High steppage
- Myopathy: Waddling

## 4. Cranial nerve Examination

Cranial Nerve	Examination
I	<ul style="list-style-type: none"> <li>▪ Smell (Certain conditions)</li> </ul>
II	<ul style="list-style-type: none"> <li>▪ Visual <b>acuity</b> (Chart, HM, LP)</li> <li>▪ Visual <b>field</b> defect (Confrontation method, 2 persons)</li> <li>▪ <b>Light reflex</b> (II → III): Direct &amp; Consensual</li> <li>▪ <b>Fundus</b>: Cherry-red spots</li> </ul>
III, IV, VI	<ul style="list-style-type: none"> <li>▪ <b>Ptois</b>: Complete, Partial, Unilateral or Bilateral</li> <li>▪ <b>Pupils</b>: Miosis or Mydriasis</li> <li>▪ <b>EOM</b>: for each eye &amp; for conjugate movements</li> <li>▪ <b>Nystagmus</b>: Horizontal, Vertical or rotatory</li> </ul>
V	<ul style="list-style-type: none"> <li>▪ <b>Motor</b>: Muscle of mastication</li> <li>▪ <b>Sensory</b>: Sensation over the face (Ophthalmic, maxillary, mandibular)</li> <li>▪ <b>Reflexes</b>: Corneal &amp; Conjunctival (V → VII), Jaw (V → V)</li> </ul>
VII	<ul style="list-style-type: none"> <li>▪ <b>Motor</b>: <ul style="list-style-type: none"> <li>- Absence of forehead wrinkles</li> <li>- Absent nasolabial fold</li> <li>- Deviation of the angle of the mouth to the healthy side</li> <li>- Dropping of the angle of the mouth (with dribbling of saliva)</li> <li>- Inability to raise the eyebrows</li> <li>- Inability to close the eye (exposure keratitis)</li> <li>- Inability to blow the cheeks</li> <li>- Inability to show the teeth</li> </ul> </li> <li>▪ <b>Sensory</b>: <ul style="list-style-type: none"> <li>- Taste sensation of the anterior 2/3 of the tongue</li> </ul> </li> <li>▪ <b>Reflexes</b>: Corneal &amp; Conjunctival (V → VII)</li> </ul>
VIII	<ul style="list-style-type: none"> <li>▪ Hearing acuity</li> <li>▪ Caloric test</li> </ul>
IX, X	<ul style="list-style-type: none"> <li>▪ Uvula position: Deviation قواع</li> <li>▪ Palatal reflex: V → VII</li> <li>▪ Pharyngeal reflex: V → VII</li> </ul>
XI	<ul style="list-style-type: none"> <li>▪ Sternomastoid (Turn head to the opposite side), Trapezius (Shoulder)</li> </ul>
XII	<ul style="list-style-type: none"> <li>▪ Tongue (Fasciculation, Deviation &amp; Power)</li> </ul>

## 5. Motor system

### a. Inspection

- **Position**
  - Frog-leg
  - Scissoring
- **State of the muscle**
  - Wasting
  - Pseudohypertrophy
- **Trophic changes**
  - Coldness & Cyanosis
  - Hair loss, brittle nails, trophic ulcers
- **Involuntary movements**
  - Chorea, Dystonia, Athetosis
  - Tremors: Kinetic or static
- **Fasciculations**
- **Skeletal deformities: Pes cavus...**



### b. Tone

- **Passive movement**
- **Shaking**
- **Gower's method**
- **Head lag**
- **Ventral suspension**
- **Frog-leg position**

#### **Hypertonia:**

- Spasticity: Clasp-knife
- Rigidity: Cog-wheel

#### **Hypotonia:**

- LMNL
- UMNL: Shock stage

### c. Power

- **Upper limb**
  - Shoulder: Flexion, Extension, Adduction, Abduction
  - Elbow: Flexion, Extension
  - Wrist: Flexion, Extension
  - Hand: Adduction, Abduction, Opposition
- **Lower limb**
  - Hip: Flexion, Extension, Adduction, Abduction
  - Knee: Flexion, Extension
  - Ankle: Dorsiflexion, Plantar flexion, Inversion, Eversion
- **Abdominal muscles**

- Dorsiflexion = Extension
- Plantar flexion = Flexion

#### **Power:**

- Passive
- Against resistance

#### **Grades of Power:**

- **0:** No movements
- **1:** Movement with gravity
- **2:** Movement against gravity
- **3:** Movement against mild R
- **4:** Movement against mod. R
- **5:** Normal strength

## d. Reflexes

### ■ Deep reflexes

#### ■ Upper limb

Reflex	Root levels	Angle	Tapping
Biceps	C 5, 6	120	On finger
Brachiocephalic	C 5, 6	120	Direct
Triceps	C 6, 7	90	Direct

#### ■ Lower limb

Reflex	Root levels	Angle	Tapping
Knee	L 2, 3, 4	90 (hanged)	Direct
Ankle	S 1, 2	120	Direct

#### ■ Pathological reflexes

Reflex	Root levels	Method	Tapping
Finger	C 8, T 1	Tapping on the 3 <sup>rd</sup>	On finger
Supraspinatus	C 3, 4	Suprespinatus	Direct

Reflex	Root levels	Angle	Tapping
Patellar	L 2, 3, 4	Knee extended	On finger
Adductor	L 4	Knee extended	On finger

#### ■ Clonus

- Ankle
- Patellar
- Wrist

#### ■ Primitive reflexes

- Grasp reflex (4 months)
- Rooting (4 months)
- Moro reflex (6 months)

### ■ Superficial reflexes

- Plantar (S 1, 2)
- Cremasteric (L 1)
- Abdominal (Upper = T 6-10 Lower = T 10-12)

#### Grades of reflexes:

- 0: Absent
- 1: Hyporeflexia
- 2: Normal reflexes
- 3: Hyperreflexia
- 4: Hyperreflexia + Clonus

#### Results of plantar reflex:

- Normal: Dorsiflex. ± fanning
- Extensor "Positive Babinski"
- Equivocal: No response

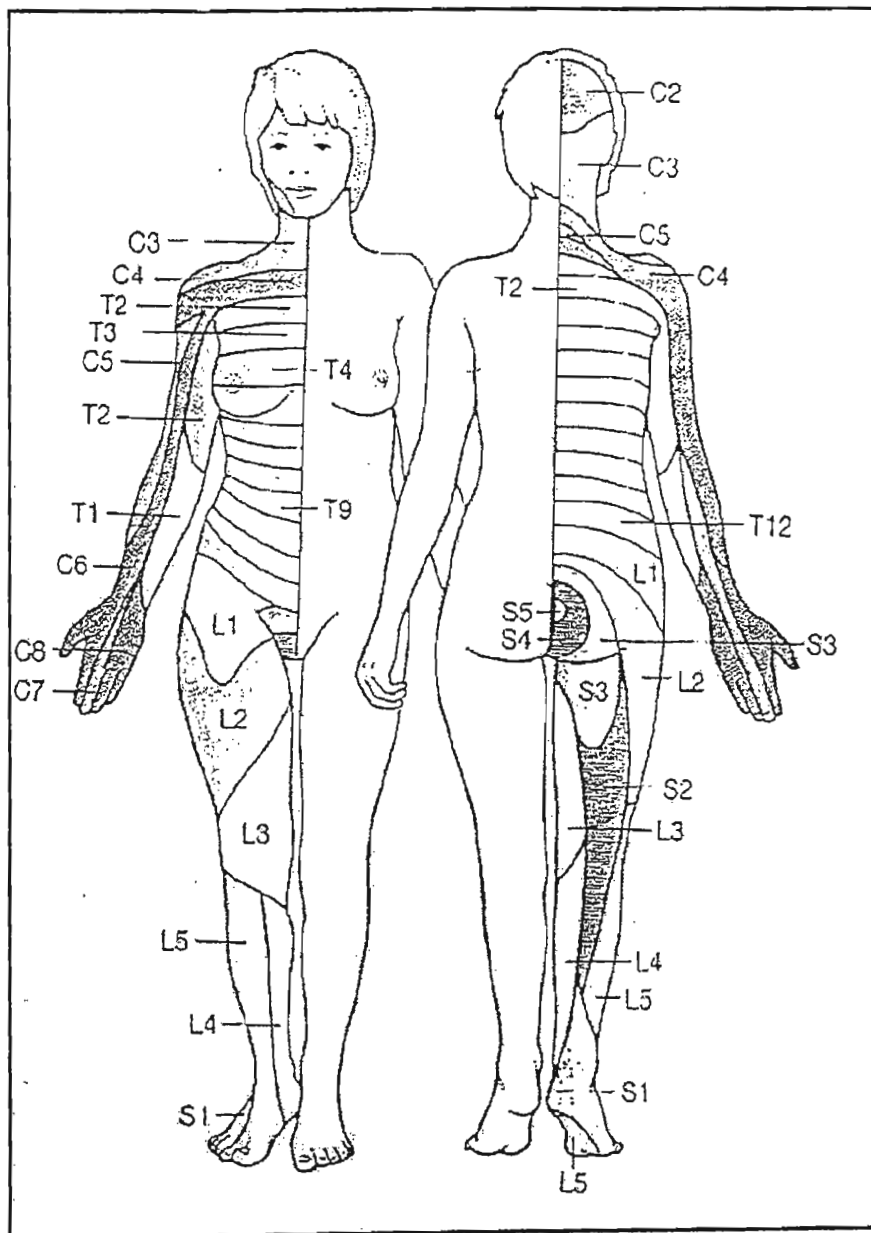
#### Important Remarks:

- Knee reflex is the easiest to elicit
- Triceps is the most difficult to elicit [Interpret your findings accordingly]
- If hyperreflexia: Try to elicit...
- Do Not say absent reflex except after....

## 6. Sensory system

### a. Superficial sensation

- Pain: Pin
- Touch: Piece of cotton
- Compare both sides
- Compare UL, Trunk, LL on the same side



#### Patterns of sensory loss:

- Sensory level
- Jacket sensory loss
- Saddle area loss
- Radicular
- Stock & Glove
- Hemihyposthesia

### b. Deep sensation

- Sense of Position & Movement
- Vibration sense
- Muscle sense
- Romberg's test

### c. Cortical sensation

- Tactile discrimination
- Tactile localization
- Stereognosis

## 7. Coordination

### a. Clinical tests:

1. Finger-to-nose
2. Finger-to-finger
3. Finger-to-doctor's finger
4. Buttoning & unbuttoning
5. Supination & pronation
6. Heal-to-knee
7. Rebound phenomenon



### b. Findings

- Kinetic tremors
- Decomposition of movements
- Dysmetria (Hypometria or Hypermetria)
- Dysdiadokokinesia

## 8. Examination of the Back

- Kyphosis
- Pott's disease of the spine
- Meningomyelocele
- Scars
- Spina bifida occulta (Lipoma, tuft of hair, sinus...)

## 9. Examination of the Cranium

- Skull circumference
- Fontanels
- Abnormal shapes (Brachycephaly, Dolicocephaly...)
- Shunt reservoir



## 10. Examination of the Neck

- Meningeal irritation signs??

	UMNL	LMNL
Paralysis	Below the level of the lesion	At the level of the lesion
State of muscles	No wasting (except late)	Early & marked wasting
Tone	Hypertonia	Hypotonia
Reflexes	Hyperreflexia	Hyporeflexia
Pathological Reflexes	May be present	Absent
Clonus	May be present	Absent
Superficial Reflexes	Lost	Lost
Fasciculations	Absent	May be present
Plantar Reflex	Positive	Equivocal

### Cranial Vs Spinal:

- Seizures, DCL, MR
- Dysmorphic facies

### LMNL:

- Myopathy: Proximal (Myotonic dystrophy)
- Neuropathy: Distal (Juvenile SMA)

# Hydrocephalus Sheet

## History

- Macrocephaly & Progressive ↑↑ in head size
- Treatment...
- Developmental history
- Nutritional history
- Motor, Sensory, Sphincteric,
- ↑↑ ICT (More prominent...)

### Shunt:

- Time
- Effect
- Complications
- Removal
- External ventricular drain

## Examination

### a. General examination

- ☑ ↑↑ Head circumference (Except in older children?)
- ☑ Bulging AF & separated sutures
- ☑ Stretched shiny scalp skin & dilated scalp veins
- ☑ Sun set sign (Downward displacement of the eyes)
- ☑ Skull percussion: Macewen sign (Cracked pot sign)
- ☑ Prominent forehead & globular face
- ☑ Meningocele or Meningomyelocele: in **Chiari** malformation



### b. Neurological examination

- Tone: Hypertonia (Spasticity)
- Power: Weakness or paralysis
- Reflexes: Hyperreflexia (± Pathological reflexes ± Clonus)
- Cranial nerves: Optic nerve atrophy (in chronic untreated patients), VI nerve palsy

Hypotonia with meningocele

## Diagnosis

- A case of macrocephaly, Hydrocephalus, most probably congenital complicated with delayed milestones, visual affection, shunt infection...
- A case of macrocephaly, Hydrocephalus, most probably post-meningitic sequel complicated with delayed milestones, visual affection, shunt infection...

## Etiology

	Obstructive	Communicating
Definition	Obstruction within the ventricular system	↓↓ CSF absorption within the subarachnoid space
Congenital	<ul style="list-style-type: none"> <li>• Aqueductal stenosis* (2)</li> <li>• Dandy-Walker malformation</li> <li>• Malformation of vein of Galen</li> </ul>	<ul style="list-style-type: none"> <li>• Arnold-Chiari malformation</li> </ul>
Traumatic	Intraventricular Hge	Subarachnoid Hge
Inflammatory	Post-meningitic gliosis	Post-meningitic gliosis
Neoplastic	Posterior fossa tumor	Leukemia (Metastatic deposits)
Others	Brain abscess	↑↑ Formation (C.P. papilloma)

# Cerebral Palsy Sheet

## History

- Delayed developmental history
- Nutritional history
- Motor, Sensory, Sphincteric, ↑↑ ICT

Not Static encephalopathy

Major insult affecting early brain development

## Examination

### a. General examination

- ☒ Head circumference
- ☒ FTT

CP is a diagnosis of exclusion

### b. Neurological examination

- ☒ Tone: Hypertonia (Spasticity), Hypotonia...
- ☒ Power: Weakness or paralysis
- ☒ Reflexes: Hyperreflexia (± Pathological reflexes ± Clonus)
- ☒ Cranial nerves:

Atonic CP

Hypotonia & brisk reflexes

## Classification

### A) Topographic

- Monoplegic
- Paraplegic
- Hemiplegic
- Triplegic
- Quadriplegic
  - Diplegic: (Spasticity is more in LL)
  - Double hemiplegic (Spasticity is more in UL)

### B) Clinical type

- Spastic
- Atonic
- Extrapyrarnidal (ataxic, dystonia & Choreoathetosis)
- Mixed

### C) Functional Classification

- Class 1: No limitation of activity
- Class 2: Mild
- Class 3: Moderate
- Class 4: Severe

### D) Associated deficits (MOTOR)

- MR
- Epilepsy
- Microcephaly
- Hearing, visual & speech abnormalities
- Behavioral & emotional disturbances
- Persistent primitive reflexes (Moro reflex)

## Diagnosis

- A case of Spastic, quadriplegic CP with severe limitation of functional activity (Class IV), associated with microcephaly, delayed developmental milestones & intractable seizures, most probably due to HIE (Obstructed labor), complicated with chest infection
- A case of spastic CP..., most probably post-meningitic sequel

Diagnosis of CP should include:

1. Etiology (Cause of CP): HIE, ICH, CNS infection...
2. Distribution
3. Type of CP (Spastic, dyskinetic, ataxic, atonic)
4. Functional activity
5. Associated deficits: MR, seizures, microcephaly...
6. Complications: Muscle wasting, deformities, contractures



# Hemiplegia Sheet

## History

- Onset: Acute (Vascular), Gradual (Neoplastic)
- Course: Regressive (vascular), Progressive (Neoplastic)
- Distribution: Side (Rt or Lt), Distal > Proximal, Progravity > Antigravity
- State: Spastic or flaccid
- Sensory, ↑↑ ICT, Sphincteric
- Pain & blood transfusion
- Cardiac symptoms: RHD ( ), CHD "Cyanotic" ( )
- Trauma, Edema, prolonged recumbency
- Thrombotic & bleeding tendency

## Examination

### According to the STAGE:

- Acute cases pass into 2 stages of paralysis (Shock stage & Spastic stage)
- Chronic cases pass directly into the spastic stage

### A) Shock stage

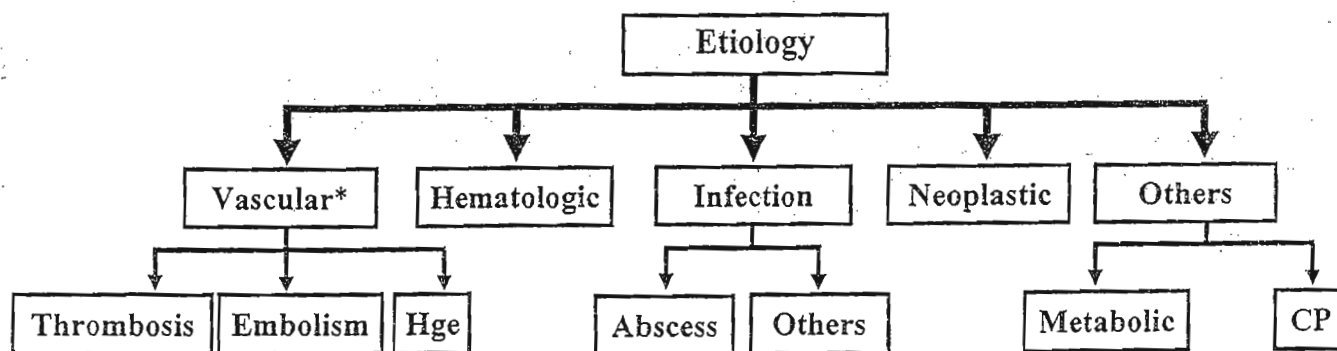
- Weakness or paralysis
  - Hypotonia & hyporeflexia + (+Ve Babinski sign)
  - One side of the body
- Duration: 2-6 wks

### B) Stage of spastic paralysis

- Weakness or paralysis
  - One side of the body, Distal > Proximal
  - Paralysis is more in the Progravity muscles
  - Hypertonia (Spasticity) is more in the antigravity muscles
  - Hyperreflexia, pathological reflexes (Finger, patellar, adductor reflexes)
  - Clonus (ankle, patellar)
  - +ve Babinski sign
- Gait: Circumduction

- Antigravity muscles
  - UL flexors
  - LL extensors
- Progravity muscles
  - UL extensors
  - LL flexors

### C) Other Manifestations (According to the... )



## Common Causes

## Definition

Weakness or paralysis of one side of the body due to pyramidal tract lesion at any point from its origin in the cerebral cortex down to the 5<sup>th</sup> cervical segments

→ 3 levels [Spinal cord, brain stem & cerebral]

## Spinal Cord (Brown-Sequard syndrome)

### Site of the Lesion

Hemisection of the spinal cord (C1-C5)

### Clinical Picture

#### a. At the level (*Root affection*)

☒ **Motor:** Ipsilateral paralysis of the muscles supplied by the affected segments...

☒ **Sensory:** Ipsilateral loss of all sensations in the area supplied by the affected segments

#### b. Below the level

☒ **Motor:** Ipsilateral hemiplegia

☒ **Sensory:**

▪ Ipsilateral deep sensory loss

▪ Contralateral loss of pain & touch sensation

▪ ↓↓ Touch on both sides

## Brain Stem

### Site of the Lesion

One side of the brain stem

### Clinical Picture

a. At the level: Ipsilateral cranial nerve affection (LMN nature)

b. Below the level: Contralateral hemiplegia (UMN nature)



**Crossed  
Hemiplegia**

## Cerebral

### Site of the Lesion

Lesion in the cerebral hemisphere (Cortical, subcortical or capsular)

### Clinical Picture

a. Contralateral Hemiplegia

b. Contralateral paralysis of VII & XII nerves

### Level

	Cortical	Subcortical	Capsular
Features	Coma Convulsions Aphasia (Dominant hemisphere)	The same as cortical	No Coma No Convulsions No Aphasia
Extent	Usually monoplegia (Incomplete) Hemihyposthesia (Parietal lobe)	More extensive	Complete hemiplegia Hemihyposthesia

Diagnosis of Hemiplegia

5

### Hemiplegia:

- 
- 
- 
- 
-

## Diagnosis

- A case of RHD (MS, pulmonary HTN...) complicated by Lt sided spastic capsular hemiplegia, most probably vascular embolic secondary to intracardiac thrombus

### Hemiplegia in RHD:

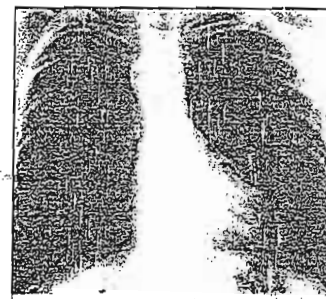
- Thrombosis
- Infective endocarditis
- Arrhythmias (AF...)

- A case of congenital cyanotic HD with ↓↓ PBF most probably Fallot tetralogy complicated by Rt sided spastic capsular hemiplegia, most probably due to intracranial thrombosis (↑↑ Viscosity)

### Hemiplegia in Fallot:

- Thrombosis
- Brain abscess
- Infective endocarditis

- A case of congenital cyanotic HD with ↓↓ PBF most probably Fallot tetralogy complicated by Rt sided spastic capsular hemiplegia, most probably due to intracranial thrombosis (↑↑ Viscosity)



- A case of CHA "Sickle cell anemia" complicated by Rt sided spastic capsular hemiplegia, most probably due to intracranial thrombosis 2ry to ↑↑ Viscosity (Sickling)

### Hb Polymerization

- Rt sided spastic capsular hemiplegia, most probably due to intracranial thrombosis 2ry to Complicated NS

### Hemiplegia in NS:

- 
-

# Paraplegia

## Definition

Weakness or paralysis of both LL

- a. **Spastic paraplegia\***: Bilateral pyramidal tract affection (Cerebral or spinal) = UMN
- b. **Flaccid paraplegia**: Cauda equina lesions & PN = LMN

## Clinical Picture (Spastic paraplegia)

a. At the level (*Root affection*) "Only in extramedullary lesions"

- ☒ **Motor**: Ipsilateral paralysis of the muscles supplied by the affected segments...
- ☒ **Sensory**: Ipsilateral loss of all sensations in the area supplied by the affected segments
- ☒ **Pain**: in vertebral lesions

b. Below the level

- ☒ **Motor**: Paraplegia
  - Both LL, Distal > Proximal
  - Paralysis is more in the progravity muscles
  - Hypertonia (Spasticity) is more in the antigravity muscles
  - Hyperreflexia, pathological reflexes (Patellar & adductor reflexes)
  - Clonus (wrist, ankle, patellar)
  - +ve Babinski sign

- **Acute cases**: Shock & spastic stages
- **Chronic cases**: Spastic stage

☒ **Sensory & sphincteric**:

- Extramedullary lesions: Sensory level below which, all sensation are lost
  - Early loss of sensation in the saddle area
  - Late bladder disturbances
- Intramedullary lesions: Jacket sensory loss of dissociated nature (Pain & Temp.)
  - Sacral spare
  - Early bladder disturbances

## Diagnosis of Paraplegia

6

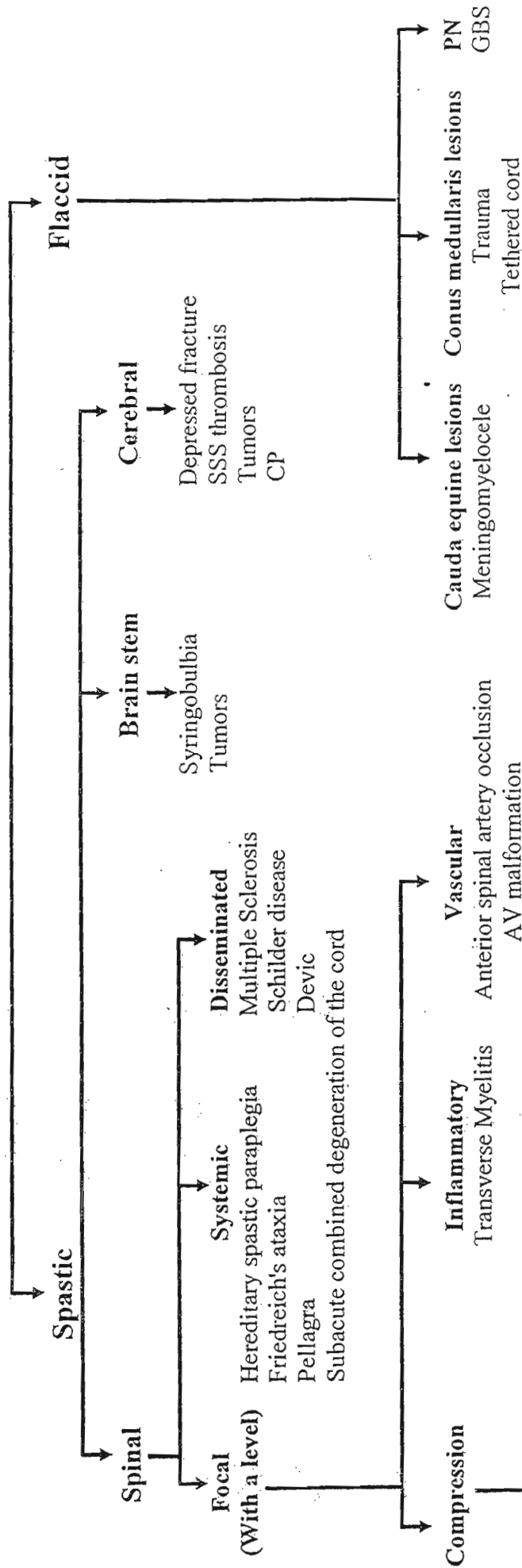
1. Type
2. Level
3. Focal (Level) or Not
4. ?Transverse myelitis ?Vascular
5. Compression (Extra- Vs Intra-)
6. Vertebral

## Common Causes

- 
- 
- 
- 
- 

	GBS	Transverse Myelitis
Tone		
Reflexes		
Pathological Reflexes		
Clonus		
Sensation		
Plantar Reflex		

# Paraplegia



	Extra-medullary	Intra-medullary
Pain	Present	Absent
UB	Late	Early
Motor	Asymmetric	Symmetric
Level	Sensory level	Jacket sensory loss
Type	All	Dissociated nature
Saddle	Early	Late
Sphincteric	Late	Early

# Floppy Infant

## Definition

Infant with severe persistent hypotonia

## Etiology

### A) Central Hypotonia

1. Chromosomal
  - Trisomies: Down syndrome
  - Prader-Willi syndrome
2. Peroxisomal [Zellweger \$ (Cerebrohepato renal)]
3. Atonic CP
4. Kernicterus
5. HIE
6. ICH
7. Familial Dysautonomia
8. Oculocerebrorenal syndrome (Lowe syndrome)
9. Gangliosidosis
10. Leukodystrophy (Which types??)

#### Atonic CP

Hypotonia & brisk reflexes

### B) N/M causes (Motor unit disorders)

1. Spinal cord disorders
2. AHC disease: Weding-Hoffmann syndrome (SMA type1)
3. Polyneuropathy
  - HMSN Type 3 (Dejerine Sottas Disease)
  - Giant Axonal Neuropathy
  - Congenital Hypomyelinating Neuropathy
4. N/M junction disorders
  - Congenital (Familial) myasthenia: ( $\downarrow\downarrow$  or absent ACh receptors)
  - Transient neonatal myasthenia: Transplacental passage of Ab (Myasthenic mother)
  - Infant Botulism
5. Myopathy
  - Benign congenital hypotonia
  - Congenital myopathy (Myotubular, Nemaline-rod, CMFTD)
  - Metabolic: GSD type 2 (Pompe), mitochondrial myopathy
  - Muscular Dystrophy: Congenital muscular dystrophy, Myotonic dystrophy

## Diagnosis (أسئلة ٣)

### ☒ Diagnosis of floppy infant (Hypotonia)

- Head lag
- Ventral suspension
- Frog-leg position

### ☒ Clues to the diagnosis of cerebral hypotonia

- DCL
- Seizures
- Dysmorphic facies
- Normal or brisk reflexes

### ☒ Clues to the diagnosis of Motor unit disorders

- Fasciculations
- Hyporeflexia

## Diagnosis

A case of floppy infant, N/M disorder, AHC disease, most probably SMA 1 (Weding-Hoffmann syndrome), complicated with delayed milestones, chest infection...

# Muscular Dystrophy

## Essential Criteria

- Primary myopathy
- Progressive
- Genetic (XLR, AR, AD)
- Degeneration

- Duchenne
- Becker
- Emery-Dreifuss
- Limb girdle
- Facioscapulohumeral
- Congenital
- Myotonic

## Duchenne Muscular Dystrophy

### Incidence

- The most common hereditary N/M disease
- 1:3.600 liveborn ♂

### Etiology

- XL-R (Mother is carrier with ↑↑ CK "Lyon hypothesis")
- Dystrophin gene

### Clinical Picture

A) Infancy: Asymptomatic or mild hypotonia

B) Childhood

a. Skeletal Muscles: Weakness

- LMNL (Hypo-, hypo-, pseudohypertrophy)
- Bilateral, symmetrical, UL & LL, Proximal > Distal [Shoulder & pelvic girdles]
- Winging of the scapulae
- Pot-belly abdomen
- Exaggerated lumbar lordosis
- Waddling gait
- Gower's sign (Climbing rest)
- No affection of EOM, hand muscles or sphincters

b. Cardiomyopathy

c. Intellectual Impairment (25%)

### Investigations

- Serum CK: Markedly ↑↑ (Thousands), AST
- NCV, EMG, Muscle biopsy
- CXR, ECG, Echo-
- Genetic analysis & carrier detection, Antenatal diagnosis

### Treatment (Supportive)

- Nutritional support, Myoblast transplantation, Gene therapy

### Prognosis

Death before 20 yrs

### Pseudohypertrophy

1. Calf muscle
2. Gluteus maximus
3. Quadriceps
4. Deltoid
5. Supra & infraspinatus
6. Tongue

### Purely Motor

### Proximal muscle weakness:

1. Climbing stairs
2. Combing hair
3. Getting in & out of bed, chair or car
4. Gower's sign

### Cause of Death

1. HF
2. Respiratory Failure
3. Pneumonia

5

4

## Becker Muscular Dystrophy

### As Duchenne but

- Onset: Later
- Course: Slower
- Intellectual impairment: Less
- Survival: More

## Other Muscular Dystrophy

XL-R	AR	AD
Duchenne	Limb-Girdle	Facioscapulohumeral
Becker	Congenital	Myotonic Dystrophy
Emery-Dreifuss		

# Neurodegenerative Diseases

Usually fatal

## Definition

Disorders characterized by **progressive deterioration** of previously acquired neurologic functions (Intellectual, motor, sensory) with loss of speech, vision & hearing, often associated with seizures & feeding difficulties

## Classification

A) **Gray matter diseases** [Early manifestations = Seizures, DCL, Visual & intellectual]

a. **Storage diseases**

- GM1 Gangliosidosis
- GM2 Gangliosidosis
  - Tay-Sachs
  - Sandhoff
- Gaucher
- Niemann-Pick
- Neuronal ceroid lipofuscinoses

Disease		Enzyme Defect
Gaucher		$\beta$ -Glucocerebrosidase
Niemann-Pick		Sphingomyelinase
GM <sub>1</sub> Gangliosidosis		$\beta$ -Galactosidase
GM <sub>2</sub>	Tay-Sachs	Hexosaminidase A
	Sandhoff	Hexosaminidase A & B
NC lipofuscinoses		Palmitoyl-protein thioesterase

b. **Non-storage diseases**

- Leigh disease
- Alpers (Hypotonia, seizures, hepatomegaly)

B) **White matter diseases** [Early manifestations = Motor dysfunction, hypotonia, spasticity]

a. **Leukodystrophies** (Loss of previously malformed myelin sheath)

b. **Demyelinating diseases** [ADEM, MS...] 5

Disease	Main Clinical manifestations
Canavan	Macrocephaly
Alexander	Macrocephaly
Metachromatic LD	Regression & ataxia
Krabbe disease	Spasticity, $\uparrow\uparrow$ irritability & $\uparrow\uparrow$ crying
Kinky hair disease (Menkes)	Hypotonia, seizures
N. Adrenoleukodystrophy	Hypotonia, seizures
XL Adrenoleukodystrophy	Onset = 3-4 yrs (academic $\downarrow\downarrow$ , seizures, spasticity)

C) **Other degenerative brain diseases:**

- Friedreich's ataxia
- Ataxia telangiectasia
- Abetalipoproteinemia (Acanthocytosis)
- Huntington chorea
- Wilson disease
- Idiopathic torsion dystonia
- Hallervorden-Spatz
- Subacute sclerosing panencephalitis

## Diagnosis

1. **Neurodegenerative**

2. **Type**

3. **Etiology**

### Cherry-red spots

- GM1
- GM2
  - Tay-Sachs
  - Sandhoff
- Niemann-Pick
- Metachromatic LD
- Sialidosis



# Neurocutaneous Syndromes

## Definition

They are a group of disorders characterized by involvement of the CNS & skin

## Neurofibromatosis

### Classification

- NF type 1: AD<sup>17</sup>. It is the most common neurocutaneous syndrome (1: 4000)
- NF type 2: AD<sup>22</sup>

### Neurofibromatosis Type 1

#### Diagnostic Criteria

1. Café-au-lait patches (100% of patients)
  - Prepubertal:  $\geq 6$  macules; 5 mm in diameter
  - Postpubertal:  $\geq 6$  macules; 15 mm in diameter
2. Axillary freckling: Hyperpigmented areas
3.  $\geq 2$  Iris Lisch nodules (Hamartomas)
4.  $\geq 2$  neurofibroma or 1 plexiform neurofibroma
5. Osseous lesions (e.g., kyphoscoliosis)
6. Optic glioma
7. 1<sup>st</sup> degree relative with NF-1

#### DD of café-au-lait spots:

1. Neurofibromatosis
2. Fanconi anemia
3. McCune Albright
4. Chediak-Higashi
5. Ataxia telangiectasia
6. Bloom
7. Tuberous sclerosis

2/7

#### Complications

1. Learning disabilities
2. Psychological
3. Seizures
4. Hydrocephalus
5.  $\uparrow\uparrow$  incidence of brain tumors

### Neurofibromatosis Type 2

#### Diagnostic Criteria

1. Bilateral acoustic neuromas (8<sup>th</sup> nerve schwannoma)
2. Unilateral acoustic neuroma + parent or sibling with NF-2

1/2

### Von-Hippel-Lindau Disease

#### Etiology

AD

#### Clinical Picture

1. Neurological
  - Cerebellar hemangioblastoma: Cerebellar ataxia
  - Spinal cord hemangioblastoma: Sensory ataxia
2. Retinal angiomas
3.  $\uparrow\uparrow$  incidence of tumors
4. Renal cysts

Cryotherapy  
Laser photocoagulation

### Refsum Disease

### Ataxia telangiectasia

# Tuberous Sclerosis

## Etiology

AD

## Pathology

Subependymal tubers that may become calcified

## Clinical Picture

### 1. Neurological

- Convulsions (Infantile spasm\*, myoclonic epilepsy...)
- Mental retardation (60-70 %)
- Behavioral abnormalities (e.g., autism, rage...)

Any type of convulsions except petit mal

### 2. Skin manifestations

- Hypopigmented macules ( $\geq 3$ )
- Sebaceous adenoma (nose & cheeks)
- Shagreen patches: rough raised lesions with orange-peel surface (Lumbosacral area)

DD: acne

### 3. $\uparrow\uparrow$ incidence of brain tumors

### 4. Hydrocephalus

### 5. Heart: Rhabdomyoma (slow spontaneous resolution is common!!)

### 6. Renal angiomyolipoma & renal cysts

### 7. Pulmonary lymphangiomatosis

# Sturge-Weber Disease

## Etiology

Sporadic

## Pathology

- Abnormal cerebral vascularization ( $\uparrow\uparrow$  vascularization of the leptomeninges)
- Pressure atrophy of the underlying brain tissue

## Clinical Picture

### 1. Neurological

- Convulsions (Contralateral side)
- Hemiplegia/paresis
- Learning disabilities

### 2. Skin manifestations: Facial nevus (port-wine)

### 3. Glaucoma & buphthalmos

Always involves the upper face but may involve lower face & trunk

## Investigations

- Skull X-ray: Serpentine appearance (occipitoparietal region)
- CT Brain

# Incontinentia pigmenti

## Etiology XL-D

## Clinical Picture

### 1. Neurological: Seizures, mental retardation

### 2. Skin manifestations: vesicular, hypopigmented or pigmented lesions

Hypophosphatemic rickets  
Alport syndrome  
Incontinentia pigmenti

# PHACE Syndrome

Posterior fossa malformations, Hemangioma, Arterial anomalies, Coarctation, Eye anomalies

# Linear Nevus Syndrome

Mental retardation & seizures + Facial nevus (forehead)

# Mucopolysaccharidosis

## Biochemistry

- ☒ **Monosaccharide:** Glucose, Galactose, Fructose
- ☒ **Disaccharide:** Maltose, Lactose, Sucrose
- ☒ **Polysaccharide:**
  - Homo-: Glycogen, Starch, Inulin, Agar
  - Hetero-: Glycosaminoglycans (= MPS)

### **GAG:**

- Chondroitin sulfate
- Dermatan sulfate
- Keratan sulfate
- Heparan sulfate
- Hyaluronic acid

## Definition

- Group of inherited disorders caused by incomplete degradation of & storage of GAG
- Lysosomal diseases
- Hurler is the most common & most severe

## Mode of Inheritance

All are AR except Hunter (Type II)

## Clinical Picture

- Normal at birth, Why???
- Progressive course
- Nasal discharge
- All have corneal Clouding except...
- Deafness in Type...
- Hernia (Recurrent)
- Main organs: Bones, Cartilages, Joints, Tendons, CT, Skin, CNS

## Classification

With...	Without...
Hurler syndrome (Type I-H)	Morquio syndrome (Type IV)
Hunter syndrome (Type II)	Scheie syndrome (Type V = Type I-S)
Sanfilippo syndrome (Type III)	Maroteaux-Lamy syndrome (Type VI)

- Sly disease (Type VII): Early infantile onset
- Type IX: Periarticular soft tissue masses & short stature

## Dysostosis Multiplex

- Radiological changes
- Features
  - Skull: Macrocephaly, Dolicocephaly, J-shaped sella turcica
  - Clavicles: Thickening of the medial 1/3
  - Ribs: Spatulated (oar-shaped)
  - Vertebrae: Ovoid with anterior beaking
  - Iliac bones: Flaring
  - Radius & Ulna: Abnormal with V-shaped articulation
  - Metacarpals: Pointed proximally (5<sup>th</sup>\*)
  - Phalanges: Pointed distally (bullet-shaped)

## Diagnosis

- ☒ **Clinical**
- ☒ **Radiological:** Dysostosis multiplex
- ☒ **Urinary GAG**
- ☒ **Enzyme assay** (Serum, WBC, Fibroblasts):  $\alpha$ -L-Iduronidase in MPS-I-H

## Hurler Syndrome

1. At birth: Normal
2. 1<sup>st</sup> year:
  - Persistent nasal discharge & obstruction
  - MR
  - HSM
  - Kyphosis
3. After the 1<sup>st</sup> year
  - Nasal discharge, MR, HSM, Kyphosis
  - Coarse facies: Large head, hypertelorism, depressed nasal bridge, low set ears, thick lips
  - Coarse hair
  - Cardiac: Cardiomyopathy, coronary stenosis
  - Skeletal: Joint stiffness, claw hand, kyphosis, hernia, X-rays (Dysostosis multiplex)

$\alpha$ -L-Iduronidase

Most common  
Most severe

## Scheie Syndrome

1. Previously called Type V
2. C/P appears after the age of 5 years
3. Corneal clouding
4. Claw hand
5. Carpal tunnel syndrome
6. Aortic regurgitation
7. Normal mentality

Mildest

5

## Hunter Syndrome

1. XLR
2. As Hurler but milder
3. No Corneal clouding
4. Deafness
5. Hydrocephalus

XLR الوحيد  
No corneal clouding الوحيد

## Sanfilippo Syndrome

1. Rapid neurological deterioration
2. Severe MR
3. Minimal findings

Neurological

## Morquio Syndrome

1. Short stature
2. Skeletal: Kyphosis, flat feet, genu valgum, platyspondyly
3. HSM, corneal clouding...
4. Separated teeth, broad mouth

Skeletal

## Maroteaux-Lamy Syndrome

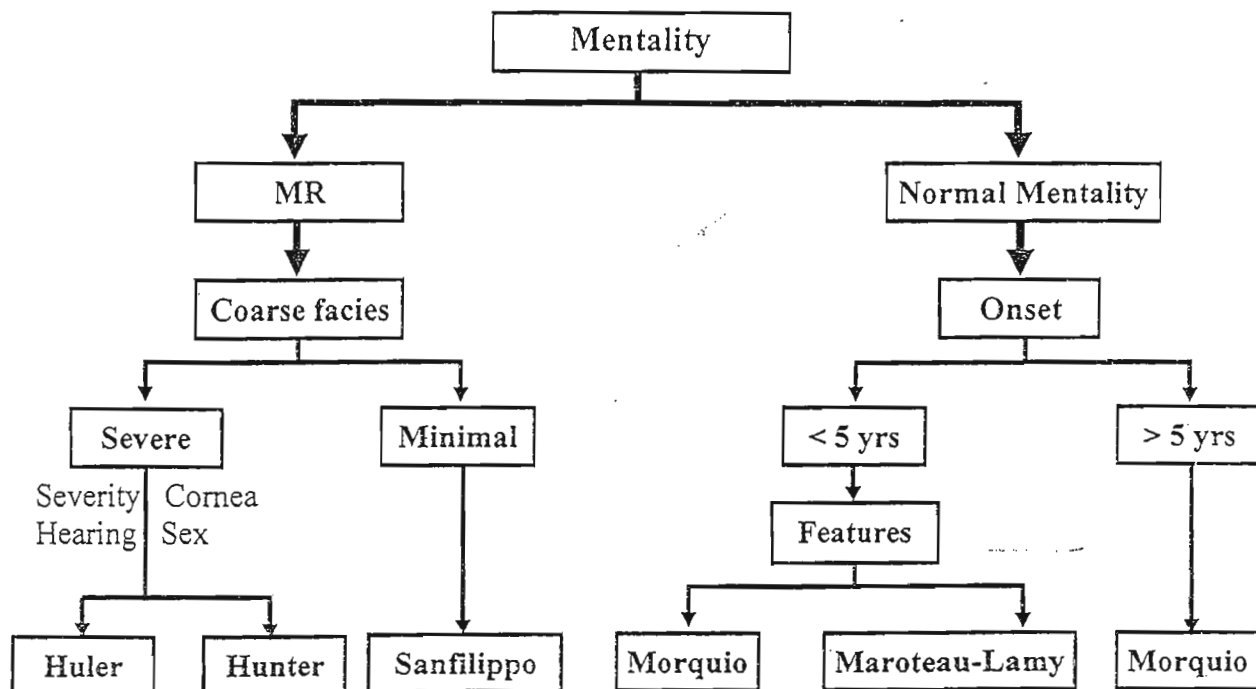
1. As Hurler but delayed onset & slower course
2. Normal mentality

No MR

## Sly Syndrome

## MPS -IX

## Clinical Approach to a case of MPS



# Short Stature

## Definition

Height more than 2 SD below the mean height for age & sex or < 5<sup>th</sup> percentile.

**Pathologic short stature:** Height >3 SD below the mean height for age & sex.

## Nomenclatures

**Lower segment:** Measured from the upper border of the symphysis pubis to the floor.

**Upper segment:** Total height – lower segment.

**Arm span:** Distance between the tips of middle fingers when the arms are fully extended.

**Supine length:** (birth to 2-3 yrs). The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard. The head should be in the "Frankfurt plane" (ear hole to lower border of eye socket).

**Standing height:** measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane".

### U/L ratio:

- At birth → 1.7 (Umbilicus is in the middle)
- At 3 yrs → 1.3
- At 7 yrs → 1 (Symphysis is in the middle)

### Arm span – height:

- 1<sup>st</sup> 7 yrs → -3
- 8 -12 yrs → zero

**Proportionate short stature:** normal values are obtained.

**Disproportionate short stature:** abnormal values are obtained.

Ratio	Short Limbs	Short Trunk
U/L	High	Low
Arm span/Height	Low	High

**Rizomelic:** proximal shortening of humerus & femur (e.g., achondroplasia)

**Mesomelic:** middle segment shortening of radius & ulna, tibia & fibula.

**Acromelic:** terminal shortening of fingers.

**Mean parental height** = (Father's height + Mother's height) / 2

**Mid Parental Height (MPH) for ♂** = Mean parental height + 7

**Mid Parental Height (MPH) for ♀** = Mean parental height - 7

**Target Centile Range (TCR) for ♂** = MPH ± 12

**Target Centile Range (TCR) for ♀** = MPH ± 11

## Etiology

1. **Familial (genetic)**
  - +Ve family history
  - Normal bone age.
  - Normal puberty.
  - Short adult height.
2. **Constitutional growth delay**
  - +Ve family history.
  - Delayed bone age.
  - Delayed puberty.
  - Normal adult height.
3. **Endocrinal**
  - Hypothalamus: Laurant-Moon Biedl
  - Pituitary: Hypopituitarism
  - Thyroid: Congenital hypothyroidism
  - Suprarenal: Cushing, CAH
  - Gonads: Precocious puberty
  - Pancreas: DM
4. **Chronic debilitating diseases**
  - CVS: CHD, RHD
  - Resp.: TB, Cystic fibrosis, asthma
  - Renal: CRF, RTA, DI
  - GIT: Malabsorption, IBD
  - Immunodeficiency
  - Hepatic: Cirrhosis, Wilson's
  - Collagen: JRA
  - Blood: Chronic hemolytic anemia
  - Infection: TB, suppurative lung S.
  - Metabolic: aa, organic acidemias
5. **Chromosomal**
  - Turner
  - Down
  - Noonan
  - Trisomy 18
6. **Congenital syndromes**
  - Prader-Willi
  - Silver-Russel
  - Cornelia De Lange (microcephaly, synophrys...)
  - Progeria
7. **Metabolic**
  - Aminoacidopathies
  - Organic acidemias
  - Storage diseases (Gaucher, NP...)
  - Minerals: Cu, Fe...
8. **Psychological (deprivation) dwarfism**

Disturbed child-mother or family relation leads to functional hypopituitarism (unknown mechanism). Bone age is delayed.
9. **Malnutrition**
10. **Skeletal (=Causes of Disproportionate short stature)**
  - Rickets
  - Achondroplasia (large head, short limbs & normal trunk) + Normal mentality
  - Hypochondroplasia (normal head + Features are not prominent as achondroplasia)
  - Osteogenesis imperfecta (osteoporosis + multiple fractures + blue sclera + hearing ↓↓)
  - Mucopolysaccharidoses
  - Chondroectodermal dysplasia (short limbs + ectodermal dysplasia + polydactyly + CHD)
11. **Primordial short stature (LBW short stature)**
  - IUGR (Congenital infections, Congenital malformation, placental insufficiency)
  - Silver-Russel syndrome (triangular face, incurved 5th finger, hemihypertrophy)
  - Seckel syndrome (bird-headed dwarfism)
12. **Drugs: Steroids**

## Approach to a case of short stature

### (A) History:

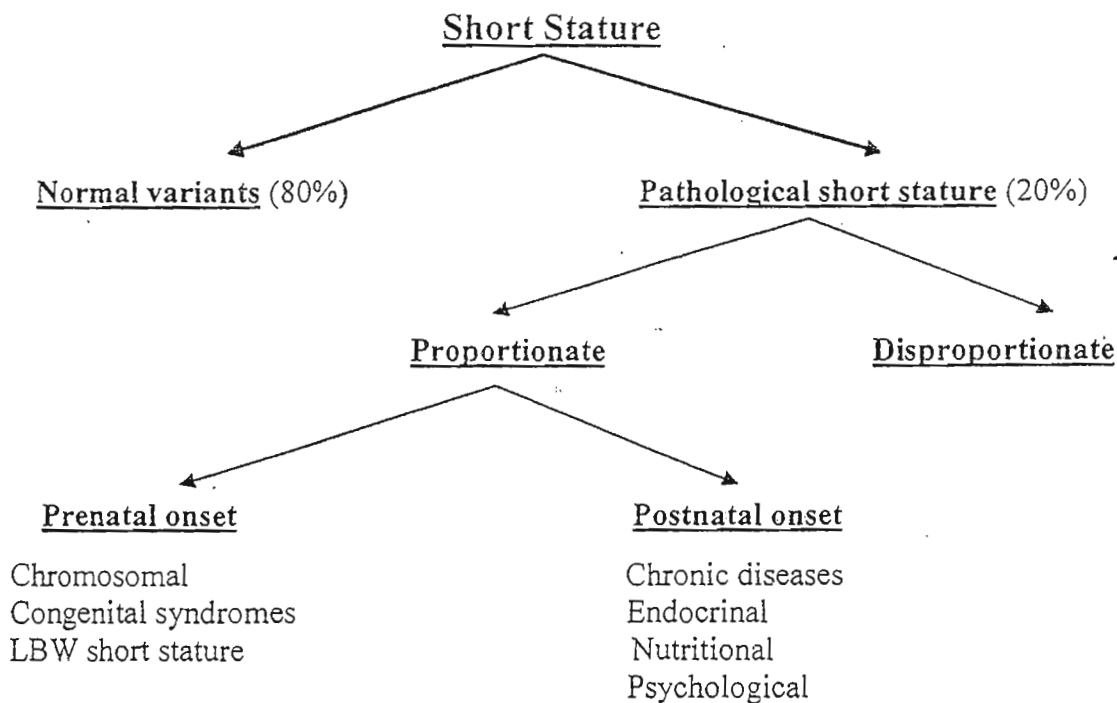
- Symptoms of different system affection
- Nutritional history
- Perinatal history: Birth length & weight, causes of IUGR
- Psychological assessment
- Parental heights & TCR

### (B) Physical examination:

- Measure height/length, US & LS, arm span → Proportionate or disproportionate
- Manifestations of chromosomal abnormalities (e.g., Turner...), congenital syndromes (e.g., Prader-Willi), hypopituitarism (microphallus)
- Complete system examination.

### (C) Investigations:

- CBC, ESR, UA, electrolytes, KFTs, LFTs
- Karyotyping is routine in all ♀ with short stature
- Bone age (Lt wrist X-ray): normal in familial cases & skeletal dysplasia
- Imaging: CT, MRI
- Investigations of endocrinal causes (start with thyroid). See before





# Down syndrome (Trisomy 21)

## Definition

It is ~~numerical~~ chromosomal aberration (Trisomy 21) in which the cell contains 3 copies of chromosome number 21 instead of 2 (i.e., Extra chromosome 21)

**Incidence** 1: 700

### Non-disjunction:

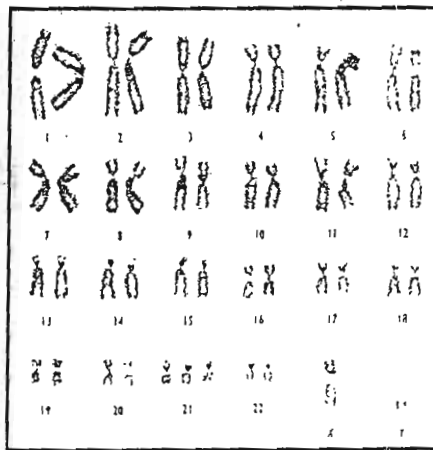
1. 20 yr = 1/2000
2. 30 yr = 1/1000
3. 40 yr = 1/100
4. 50 yr = 1/10

## Genetic Types (discuss)

- ☒ Non-disjunction (95 %): The extra-21 chromosome is usually of maternal origin (97 %) [Non-disjunction during maternal meiosis]
- ☒ Translocation (4%): The extra-21 chromosome is translocated to another acrocentric chromosome (group D 13-15 or group G 21-22)  
One of the parents should be translocation carrier [Balanced translocation carrier]
- ☒ Mosaicism (1%): Post-fertilization event [Non-disjunction during zygote mitosis]

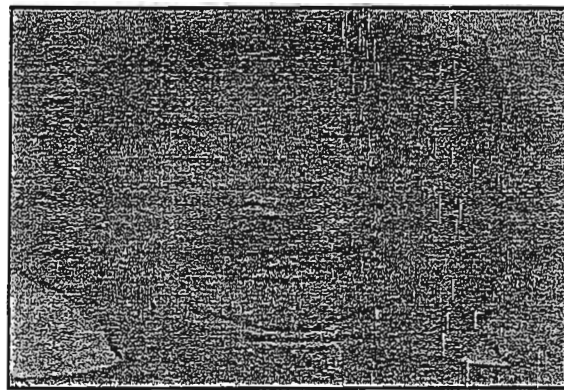
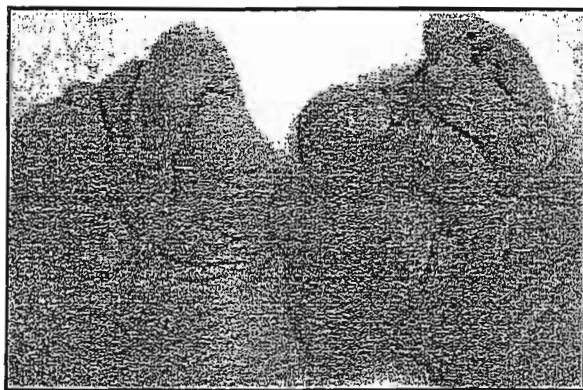
## Number of chromosomes & Recurrence risk

Type	Mechanism	No. of chromosome	Maternal age	IQ	Recurrence risk
Non-disjunction (95%)	Non-disjunction 'Maternal meiosis'	47	Age dependent	Low	↑↑ with ↑↑ maternal age
Translocation (4%)	Translocation	46	Non-age dependent	Low	a. <u>Translocation to D-group</u> 1/3 Down, 1/3 normal 1/3 translocation carrier b. <u>Translocation to chrom. 21</u> 100 % Down
Mosaicism (1%)	Post-fertilization event	46/47	± Age dependent	better	??



## Other Autosomal numerical aberrations (Trisomies)

	Trisomy 18 (Edwards S)	Trisomy 13 (Patau S)
Incidence	1/4000	1/6000
Genetic type	Non-disjunction	Non-disjunction
Features	Prominent occiput (Dolicho-) Microcephaly Eye anomalies Small ears Cardiac (VSD, PDA) Overlapping fingers (closed fist)	Microphthalmia Microcephaly Cleft lip Cleft palate Cardiac (VSD, PDA) Omphalocele
Survival	> 90% die in infancy	



## Turner Syndrome

### Genetic Types

- ☑ Non-disjunction (most common): The X chromosome is usually of maternal origin
- ☑ Mosaicism (better prognosis): 45, X / 46, XX

### Clinical picture

(A) At birth: Edema of dorsum of hands & feet

(B) Childhood:

- Short stature (mean = 143 cm)
- Webbing of the neck
- Widely spaced nipples
- Cubitus valgus (↑↑ carrying angle)
- Low posterior hair line
- Normal mentality (MR in 18%)
- Cardiac: Coarctation, bicuspid aortic valve
- Renal: Horseshoe, ectopic kidney...
- Thyroiditis (30%)
- IGT, Type II DM

(C) Puberty:

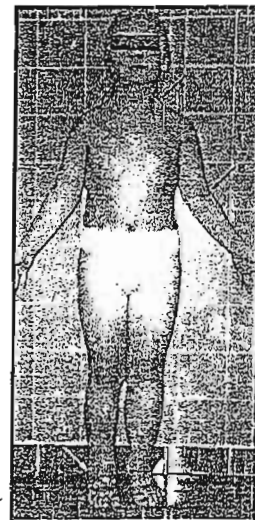
- Secondary sex characters fail to develop

### Investigations

1. ↓↓ Estrogen, ↑↑ FSH & LH
2. Karyotyping (45, X)
3. U/S, Echocardiography, Thyroid profile

### Treatment

- hGH
- Estrogens: Start at 11-12 yrs (Why?)
- Estrogen + Progesterone cyclic therapy;
- Ovum donation + IVF: ?? Fertility



## Clinical picture

A) **Delayed mental development (MR):** Delayed social smile...

B) **Delayed motor development (Hypotonia):** Delayed head support...

C) **Characteristic dysmorphic features:**

- ☒ Head: Brachycephaly, delayed closure of AF, microcephaly, silky hair
- ☒ Eye: Upward slanting palpebral fissure, epicanthal folds, cataract, squint, speckled iris
- ☒ Nose: Depressed nasal bridge
- ☒ Ears: Malformed, overfolded helix, underdeveloped ear lobule
- ☒ Mouth: Small oral cavity
- ☒ Tongue: Protruded & fissured
- ☒ Neck: Short & broad
- ☒ Hands: Short & broad + Clinodactyly + Simian crease (Single transverse palmar crease)
- ☒ Foot: Short & broad + ↑↑ gap between 1<sup>st</sup> & 2<sup>nd</sup> toes (sandal gap 97%)
- ☒ Abdomen: Distension, hernia

D) **Associated congenital anomalies:**

- a. **Cardiac (40%):** Endocardial cushion defects (AV canal), VSD, ASD, Fallot
- b. **GIT:** Duodenal atresia, annular pancreas, TOF
- c. **Renal anomalies**

50% of Down \$ have simian crease  
4% of population have simian cease

E) **Complications:**

- a. Cardiac complications (HF), recurrent chest infection
- b. ↑↑ Risk of Leukemia (AML, ALL) 10-20 fold > general population
- c. ↑↑ Risk of DM, obesity, thyroiditis & epilepsy


Do not say "a Down baby" but  
"a baby with Down syndrome"

## Investigations

- Karyotyping, CBC
- CXR, ECG, Echocardiography

## Treatment (No specific Rx-Supportive)

## Antenatal Diagnosis

Indications: 

- ☒ Old maternal age > 35 years
- ☒ Previous baby with Down syndrome
- ☒ Family history of Down syndrome
- ☒ Family history of non-disjunction
- ☒ Family history of translocation

Methods:

1. Triple test: done in maternal serum at 15-16 weeks of gestation
  - ↓↓ α-Fetoprotein
  - ↓↓ Unconjugated estriol
  - ↑↑ β-hCG
2. Dimeric inhibin; marker in maternal serum (↑↑ in Down syndrome)
3. Karyotyping:
  - Amniocentesis: 14-16 weeks of gestation
  - Chorionic villus sample: 9-12 weeks of gestation
  - Fetal cells in maternal blood
4. Fetal US
  - Nuchal Translucency thickening (NT): thickening of the fat pad at the back of the neck
  - Short femur
  - Cystic hygroma of the neck, duodenal stenosis

## Diagnosis

A case of Down syndrome most probably non-disjunction (Old maternal age) associated with CHD in the form of AV canal (or VSD) & complicated by delayed developmental milestones & recurrent chest infection...

# Chest Sheet

## History

### A) Cough

- OCD
- Timing: Nocturnal...
- Precipitating & relieving...
- Dry or Productive
- If Productive: Sputum

#### Expectoration:

1. Amount
2. Color
3. Consistency
4. Relation to position
5. Precipitating & relieving...

### B) Hemoptysis

### C) Dyspnea

### D) Chest pain

### E) TB toxemia

#### TB toxemia:

1. Night
2. Night
3. Loss
4. Loss

### F) FB inhalation

- Acute onset
- Cough, Chocking, Cyanosis

### G) Other system involvement

- Cardiac:
- Neurological:
- GIT:
- Immune:

# Chest Examination

## A) Inspection

1. **Shape:** Pigeon, Barrel-shaped, Pectus excavatum
2. **Symmetry:**
3. **Respiratory movements**
  - Rate
  - Work of breathing:
  - Working ala nasi
  - Retraction
  - Grunting
  - Accessory muscles of respiration
  - Paradoxical chest wall movements
4. **Pulsation:** Where??
5. **Scars, Pigmentation, dilated veins**

### Symmetry:

- ☒ **Unilateral bulge**
  - Effusion, Pneumothorax
- ☒ **Unilateral retraction**
  - Collapse, Fibrosis

How to DD??

Respiratory movements

## B) Palpation

1. **Mediastinal position**
  - Heart
  - Trachea
2. **Chest expansion**
3. **TVF**
  - Anterior: Infraclavicular, mammary, inframammary
  - Lateral: Upper & lower zones
  - Posterior: Suprascapular, Interscapular & Subscapular
4. **Pulsation**
5. **Palpable sounds:** Rhonchi, crepitations

TVF/VR	Pathology
↑↑	Consolidation
↓↓	Effusion/Collapse

## C) Percussion

- **Hepatic dullness**
- **Compare Rt & Lt**
- **Sites**
  - Anterior: MCL (1-6) except...
  - Lateral: Midaxillary (3-7)
  - Upper & lower zones
  - Posterior: Suprascapular, Interscapular & Subscapular
- **Percussion of special areas**
  - Kronig's isthmus: Lung apex
  - Traub's area: Fundus of the stomach
  - Bare area: 4-6
  - Tidal percussion: Liver
- **Interpretation**

Note	Pathology
<b>Resonant</b>	Normal
<b>Hyperresonant</b>	Emphysema Pneumothorax
<b>Dull</b>	Consolidation Collapse
<b>Stony dull</b>	Effusion

## Suppurative Lung Syndromes

Empyema	Lung abscess	Bronchiectasis
<p>Accumulation of pus in the pleural cavity</p> <ul style="list-style-type: none"> <li>▪ Bacterial pneumonia (Staph., pneumo-, Hib)</li> <li>▪ Trauma</li> <li>▪ Mediastinitis</li> <li>▪ Intra-abdominal abscess</li> </ul>	<p>Localized suppurative inflammation resulting in a cavity containing pus</p> <ul style="list-style-type: none"> <li>▪ Bacterial pneumonia (Staph., Klebsiella)</li> <li>▪ Aspiration of infected material</li> <li>▪ FB</li> <li>▪ Metastatic lic lung abscess (Rt sided IE)</li> <li>▪ Amebic liver abscess</li> </ul>	<p>Permanent dilatation of the bronchi with suppurative inflammation of their walls</p> <p>A) Congenital: Abnormal bronchial development</p> <p>B) Acquired: Chronic pulmonary infection</p> <ul style="list-style-type: none"> <li>▪ Cystic fibrosis</li> <li>▪ Immunodeficiency</li> <li>▪ Immotile cilia syndrome</li> <li>▪ Aspiration: FB, TOF, GERD</li> </ul>

## Interstitial Lung Diseases

Known Etiology	Unknown Etiology	Pulmonary involvement in other diseases
<ul style="list-style-type: none"> <li>▪ Hypersensitivity pneumonitis (History...)</li> <li>▪ Chronic infections</li> <li>▪ BPD</li> <li>▪ Aspiration syndromes</li> <li>▪ Lipid storage diseases</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pulmonary hemosiderosis</li> <li>▪ Bronchiolitis obliterans</li> <li>▪ Non-specific interstitial pneumonitis</li> <li>▪ Lymphocytic interstitial pneumonitis</li> <li>▪ Desquamative pneumonitis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Collagen-vascular diseases</li> <li>▪ Sarcoidosis</li> <li>▪ Histiocytosis</li> <li>▪ Malignancies</li> <li>▪ Neurocutaneous syndromes</li> </ul>

## Bronchial Asthma

Severity	Symptoms		Long-term controller treatment	Alternative
	Days with symptoms	Nights with symptoms	Preferred	Not needed
Mild intermittent	≤ 2/wk	≤ 2/month	▪ Low-dose inhaled steroids	▪ Leukotriene receptor # ▪ Theophylline SR
Mild persistent	≥ 3/ wk	≥ 3/ month	▪ Low-medium dose + LABA	▪ Low-dose + LT #
Moderate persistent	Daily	> 1/wk	▪ High-dose + LABA + Oral steroids (If needed)	
Severe persistent	Continual	Frequent		

**D) Auscultation**

- Sites:
- Comment on
  - Breath sounds: Vesicular, Harsh vesicular, Bronchial

Conducted upper airway sounds are the cause of most false +ve chest findings

	Vesicular	Bronchial
Character	Rustling	Hollow
I:E	3:1	1:1
Gap	No	Gap

- Adventitious sounds: Wheezes, Crepitations, Rub

	Wheezes	Crepitations
Timing	Expiratory ± Inspiratory	Inspiratory ± Expiratory
Character	Musical	Non-musical (Fine, Medium, Coarse)
Types	Sibilant (High-pitched) Sonorous (Low-pitched)	Consonating (Metallic) Non-consonating
Relation to cough		
Causes	<ul style="list-style-type: none"> <li>• Asthma</li> <li>• Bronchiolitis</li> <li>• FB</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Pulmonary edema</li> <li>• HF</li> </ul>

**D'Espine sign:**

Bronchial breathing on auscultation below T4 vertebra (T2 or T3 spine)

Cause: Enlarged mediastinal LN

**Pleural rub:**

- Leathery, friction sound
- Related to respiration
- Disappears on...
- Absent in...
- Cause:

- Depine sign
- Vocal resonance
  - Bronchophony: Normal sounds are heard louder & clear
  - Aegophony: Normal sounds are heard louder with nasal tone
  - Whispering pectoriloquy: Whispered sounds are heard loud & clear

**Respiratory cases in the Exam**

1. B
2. B
3. S
4. I
5. C+
6. C+
7. T

## Diagnosis

- A case of Suppurative lung syndrome; Bronchiectasis, secondary to recurrent chest infections most probably secondary to CF, complicated by pulmonary HTN (Hypoxic cor-pulmonale)

### Bronchiectasis:

- C
- I
- I

- A case of Suppurative lung syndrome; Bronchiectasis, secondary to recurrent chest infections most probably secondary to PCD, complicated by pulmonary HTN (Hypoxic cor-pulmonale)

- A case of interstitial lung disease, complicated by pulmonary HTN (Hypoxic cor-pulmonale)

- A case of wheezy chest, most probably bronchial asthma, moderate persistent according to GINA classification, complicated by short stature (Prolonged steroid therapy)

- A case of wheezy chest, most probably acute bronchiolitis, RDII

RVE	LVE	Pulmonary HTN



# Neonatal Cholestasis

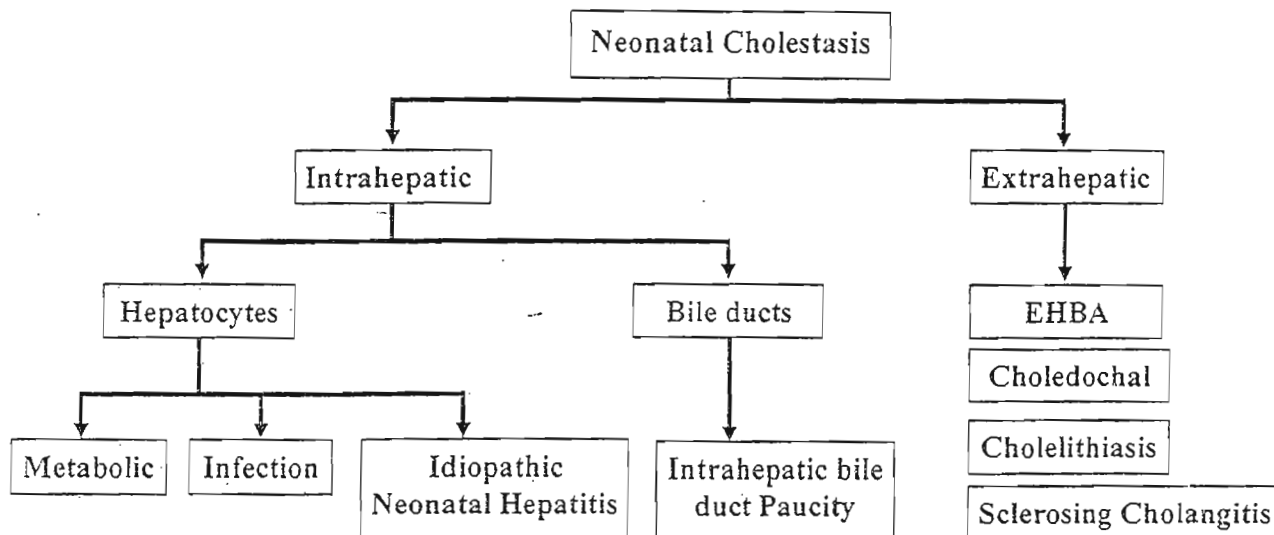
## Definition

**Cholestasis:** Any condition in which there is retention of substances normally excreted in bile with appearance of bile within the elements of the liver usually associated with 2ry liver cell injury [Practically, direct bilirubin > 2 mg% or > 20% of total bilirubin]

**Neonatal Cholestasis:** Cholestasis that persists > D14 [Always pathological]

**Obstructive jaundice:** Cholestasis due to mechanical obstruction in the hepatobiliary system

## Etiology



### A) Infections

- Neonatal sepsis
- TORCH infection
- UTI
- CMV, EBV, hepatitis viruses

### B) Metabolic

- Galactosemia
- Tyrosinemia
- $\alpha$ -1-Antitrypsin deficiency
- Cystic fibrosis
- Gaucher & Niemann-Pick
- Zellweger \$ (Cerebrohepatorenal)
- Neonatal Iron storage Disease (NISD)
- Mitochondrial hepatopathies
- Dubin-Johnson syndrome & Rotor syndrome
- Aagaens: Cholestasis + Lymphedema

### C) Cholestasis associated with TPN (Discuss)

### D) Inspissated bile syndrome (Post-hemolytic cholestasis)

### E) Bile acid synthetic defects

- Reductase
- Dehydrogenase

### F) Progressive familial intrahepatic cholestasis (PFIC)

- PFIC 1 (Byler disease):  $\downarrow\downarrow$  GGT
- PFIC 2:  $\downarrow\downarrow$  GGT
- PFIC 3:  $\uparrow\uparrow$  GGT

### G) Idiopathic neonatal hepatitis (Most common)

### H) Paucity of intrahepatic bile ducts (= Intra-hepatic biliary hypoplasia)

#### a. Non-syndromic

#### b. Syndromic (Alagille syndrome = Arteriohepatic dysplasia)

Etiology: AD (with reduced penetrance)

Pathology: Paucity of intra-hepatic bile ducts

Diagnosis:

### I) Extrahepatic: EHBA...

3/5

Alagille:	
1.	Intrahepatic paucity (100%)
2.	Vertebral arch defects
3.	Abnormal facies (Prominent forehead, Hypertriang. deep-set eyes)
4.	Ocular (Posterior embryotoxon)
5.	Cardiac (Peripheral PS, ASD)

## Pathophysiology

### A) Bile pigments ↓↓ in intestines

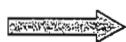
- ↓↓ Stercobilinogen → Pale stools (Clay-colored in EHBA)
- ↓↓ Urobilinogen

### B) Bile pigments ↑↑ in blood

- Jaundice
- Dark-colored urine

### C) Bile salts ↓↓ in intestines

- Fat maldigestion
- Fat malabsorption (Steatorrhea)



Vit A: Thick skin

Vit D: Rickets & osteoporosis

Vit K: Bleeding

Vit E: Hemolytic anemia, PN, myopathy

### D) Bile salts ↑↑ in blood

- Bradycardia
- Pruritus

### E) Cholesterol ↑↑ in blood: Xanthomas

### F) Biliary cirrhosis

- Liver cell failure
- Portal hypertension

## Sheet (History & Examination)

- Pathphysiology (Bradycardia, scratch marks...)
- Color of urine & stools
- HSM
- Manifestations of vitamin deficiencies
- Manifestations of congenital infection
- Cardiac murmur
- Ocular
- Lymphedema
- Abdominal mass
- Manifestations of LCF & portal HTN

## Investigations

### A) Laboratory

- ☒ Liver function tests (Liver enzymes, albumin, Bilirubin, PT, INR...)
- ☒ Reducing substances in urine
- ☒ Urine succinylacetone
- ☒ TORCH
- ☒ Serum & urine aminogram
- ☒ Sweat chloride test
- ☒ α-1-Antitrypsin

### B) Imaging

- ☒ Abdominal US →
- ☒ CT, MRI: choledochal cyst
- ☒ Scintigraphy (Tc): "Not practical"

### C) Invasive

- ☒ Duodenal aspirate: ?Bile-stained fluid
- ☒ Liver biopsy

GGT

Value of US:

1. Diagnosis of choledochal cyst
2. TC sign: suggests EHBA
3. Visualization of GB

TC sign: suggests EHBA

Live biopsy is the most important procedure in diagnosis of neonatal hepatobiliary diseases

## Diagnosis of EHBA

- Clay-colored stools (Not stained)
- HIDA: No dye
- Liver biopsy
- Operative cholangiography

# Extrahepatic Biliary Atresia

### Incidence

It is the 2<sup>nd</sup> most common cause of neonatal cholestasis

### Terminology

The term biliary atresia is not accurate.

A more correct name is **progressive obliterative cholangiopathy**

### Etiology

EHBA has postnatal onset (? infectious etiology; Reovirus)

EHBA has progressive course (ascending). This explains the high failure rate of "Kasai"

### Clinical Picture

- Clay-colored stools (pigmented stools can be detected in the first few days)
- Consistently pigmented stools is against the diagnosis

Kasai has better success rate if done < 8 wks

### Diagnosis

Early Diagnosis is critical

### Treatment

#### A) Medical Rx

#### B) Surgical Rx: Kasai operation (Transection of the porta hepatis + anastomosis to the bowel)

##### ▪ Postoperative management

- Antibiotics: Cefotaxime (100 mg/Kg/day)
- Antipyretics: Paracetamol (10-15 mg/Kg/dose), PO, Rectal, IV
- Steroids: Hydrocortisone followed by oral Prednisolone (1mg/Kg/day). Why?

Avoid Ceftriaxone

##### ▪ Post-Kasai fever

- Consider & manage as cholangitis until proved otherwise
- CBC, CRP, Blood C&S, LFT, GGT
- Antibiotics...

Always suspect...

## Management of Neonatal Cholestasis

### A) Medical

1. Nutrition: Formula containing medium-chain triglycerides (Pregestimil)

2. Fat-soluble vitamins

- Vit A: 50,000 IU twice weekly
- Vit D: 300,000 IU/ 2 months (Check urine Ca/Cr ratio)
- Vit K: 10 mg/week PO (Use Konakion MM ampoules)
- Vit E: 100 IU/day

Vitamin K is the initial Rx of cholestasis

3. Water-soluble vitamins, Micronutrient supplementation: Ca, P, Zn

4. Choleretics: Ursodeoxycholic acid (Ursofalk): 15-30 mg/Kg/day single daily dose

5. Pruritus

- Ursodeoxycholic acid
- Cholestyramine (4-16 g/day)
- Rifampicin
- Phenobarbitone
- Carbamazepine
- Cool baths, topical creams, anti-histamines

6. Management of complications: portal hypertension, LCF

7. Liver transplantation

### B) Surgical

1. Excision of choledochal cyst

2. Kasai operation (Hepatoportoenterostomy)

Cholestran  
4 gm

# Nephrotic Syndrome Sheet

## History

- Generalized edema: OCD
- Urine: Color, volume
- HTN: Headache, episatxis?
- RD
- Abdominal pain
- Infections
- Thromboembolic manifestations
- Response to Rx
- Recurrence (& Relation to Rx dose)
- Hepatic, Cardiac, allergic symptoms
- Nutritional history
- Other: ...???

### Abdominal pain in NS:

1. Intestinal wall edema
2. Mesenteric hypoperfusion
3. Peritonitis
4. Pancreatitis
5. Peptic ulcer (Gastritis)
6. Pvelonephritis

### RD in NS:

1. Pneumonia
2. Pleural effusion
3. Marked ascites

## Examination

- Vital signs: BP, Temperature, HR, RR
- Generalized edema:
- Others...???
- S
- S
- Other systems...

## DD of NS

### 1. Causes of generalized edema

	Mechanism	C/P
Nutritional	Hypoalbuminemia (↓↓ OP)	Kwashiorkor (Ascites is rare)
Hepatic	Hypoalbuminemia (↓↓ OP)	Jaundice, hepatomegaly...
Cardiac	↑↑ Venous pressure	Tachycardia, Tachypnea, Tender hepatomegaly
Allergic	↑↑ Capillary permeability	History + Itching + Urticaria

### 2. MCNS Vs non-minimal NS

	MCNS	Non-MCNS
Age		
Hematuria		
HTN		
Renal function		
Complement		
Selectivity (Proteinuria)		
Renal biopsy		
Response to steroids		

## Diagnosis

- A case of Generalized edema, renal, NS, most probably MCNS
- A case of Generalized edema, renal, NS, most probably non-MCNS complicated with chest infection, steroid toxicity...
- A case of Generalized edema, renal, NS, non-MCNS...

## Nephrotic Syndrome during the 1<sup>st</sup> year

### Definition

Congenital NS: onset during the first 3 months of life

Infantile NS: onset during the first year (4-12 months)

### Etiology

1. Congenital NS of the Finnish type\* (most common)
2. Congenital infection (CMV, Rubella, Syphilis, Toxoplasma, HBV, HIV)
3. MCNS, FSGS, membranous glomerulopathy
4. SLE
5. Diffuse mesangial sclerosis
6. Denys-Drash syndrome [Ambiguous genitalia, Glomerulopathy (diffuse mesangial sclerosis), Wilms (usually bilateral)]. Rx: bilateral nephrectomy

## Sheet

### History

- Generalized edema: OCD
- Perinatal history...
- Hypothyroidism
- Nutritional history
- Rx & response

### Examination

- Vital signs: BP, Temperature, HR, RR
- Generalized edema:
- Others...???
- C
- H

### Diagnosis

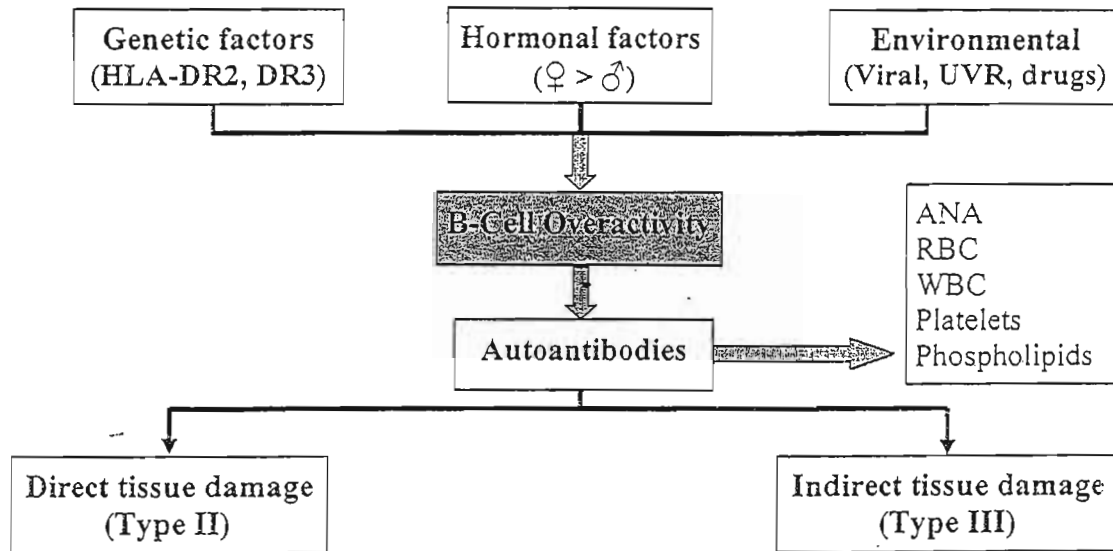
- A case of Generalized edema, congenital NS, most probably Finish type, complicated with chest infection & hypothyroidism...

# Systemic Lupus Erythematosus

## Definition

It is multisystem disease characterized by widespread organ involvement

## Pathogenesis



## Diagnostic Criteria of SLE

Criterion	Definition
1. Malar rash	Erythematous malar rash sparing the nasolabial folds
2. Discoid rash	Erythematous raised patches (scaly)
3. Photosensitivity	Unusual reaction to sunlight
4. Oral ulcers	Usually painless
5. Arthritis	Non-erosive $\geq 2$ joints
6. Serositis	a. Pleurisy: Typical pleuritic pain or rub b. Pericarditis: Rub, ECG or effusion
7. Renal	a. Proteinuria $> 0.5$ g/day b. Cellular casts (RBC, granular...)
8. Hematological	a. Hemolytic anemia b. Leukopenia ( $< 4,000/\text{mm}^3$ ) c. Lymphopenia ( $< 1,500/\text{mm}^3$ ) d. Thrombocytopenia ( $< 100,000/\text{mm}^3$ )
9. Neurological	a. Seizures: in absence of offending drugs or metabolic derangement b. Psychosis: in absence of offending drugs or metabolic derangement
10. Immunological	a. Anti-DNA antibodies b. Anti-Smith antibodies c. Anti-phospholipid antibodies (Lupus anticoagulant &/or Anticardio) d. False positive tests for syphilis
11. ANA	

## Important Remarks

- ☒ SLE is diagnosed if there are 4 out of the 11 criteria [Serially or simultaneously during any interval of observation]
- ☒ "LE cells" criterion is now deleted
- ☒ Patients suspected to have SLE should receive appropriate Rx even with  $< 4$  criteria

## Diagnosis (سؤال)

### ☒ Presentation

- Renal
- Blood
- CNS
- Joints

### ☒ Multi-system involvement

### ☒ SLE

### ☒ DD

### ☒ Steroids

4/11



4/9

## Diagnosis

# Immunodeficiency

## Suspicion of Immunodeficiency

1. Chronic
2. Recurrent
3. Resistant
4. Unusual (site, organism & severity)

Infection

### Opportunistic Organisms

- Pneumocystis carinii
- Toxoplasma
- Candida
- CMV, VZV
- Mycobacteria

B cell	T cell	Phagocyte	Complement
Sino-pulmonary Otitis media (Staph, Strept, Pneumo, Hib...)	FTT Viral infections Chronic diarrhea Candida > 6 months GVHD	Deep abscesses Ano-rectal infections	Meningitis Arthritis  <i>Angioneurotic edema</i>

## Diagnosis (أسئلة ٣)

### ☒ Immunodeficiency

- Why?
- Where?

### ☒ Type

### ☒ Etiology

## Management of Immunodeficiency

1. Avoid live vaccines
2. Avoid blood transfusion (use irradiated blood, why?)
3. Personal hygiene
4. Prophylactic & therapeutic antibiotics
5. IVIG for hypo- or agammaglobulinemia (400 mg/Kg at monthly intervals), Complications?
6. HSCT, Complications?

IVIG is contraindicated in selective IgA deficiency

## Joint Examination

### A) Inspection

1. Position
2. Swelling
3. Redness
4. Deformity
5. Range of movement

### B) Palpation


1. Tenderness
2. Synovial membrane thickening
3. Range of movement
4. Detection of effusion: Knee (Fluctuation & Patellar tap)

### C) Special Joints: T/M, Atlanto-axial, Atlanto-occipital, Sterno-clavicular, Spine



# Juvenile Rheumatoid Arthritis

## Diagnostic Criteria of JRA

1. Age at onset < 16yrs
2. Arthritis in  $\geq 1$  joint 
3. Duration  $\geq 6$  wks
4. Onset type is defined by articular involvement in the 1<sup>st</sup> 6 months of onset
  - a. Polyarthritis  $\geq 5$  inflamed joints
  - b. Oligoarthritis < 5 inflamed joints
  - c. Systemic onset: Characteristic (spiky) fever
5. Exclusion of other causes of juvenile arthritis

### Arthritis:

- Swelling or effusion OR
- 2 of the following signs: hotness, tenderness,  
 $\downarrow\downarrow$  range of movement, pain on motion

Not Red

Spiky Fever

## Clinical Picture

Morning stiffness (15-30 min), Easy fatigability, Joint pain  
 Joint swelling, hotness, tenderness but No redness

Oligoarthritis	Polyarthritis	Systemic-onset disease
Types: 1. Persistent oligo- 2. Extended oligo- ( $\rightarrow$ Poly-)	Types: 1. RF -ve* 2. RF +ve	<ul style="list-style-type: none"> <li>- Daily spiky fever <math>\geq 2</math> wks (high fever with <u>normal</u> intervals/day)</li> <li>- Characteristic macular rash (evanescent erythematous rash usually with the fever- trunk)</li> <li>- Arthritis may accompany or follow systemic manifestations</li> <li>- Koebner phenomenon = Cutaneous hypersensitivity to superficial trauma</li> <li>- Hip may be involved at the onset</li> <li>- HSM, LN</li> <li>- Pleurisy &amp; pericarditis</li> <li>- Leukocytosis &amp; thrombocytosis</li> <li>- ANA &amp; RF: -ve</li> <li>- <math>\uparrow\uparrow</math> ESR</li> </ul>
<ul style="list-style-type: none"> <li>- Usually affecting joints of LL (Knee &amp; ankle)</li> <li>- Asymmetric</li> <li>- Hip is almost never involved at the onset</li> <li>- Liable to chronic uveitis</li> <li>- ANA is +ve in 85-90%</li> </ul>	<ul style="list-style-type: none"> <li>- Usually affecting large &amp; small joints of LL &amp; UL (20)</li> <li>- Symmetric</li> <li>- Hip is almost never involved at the onset</li> <li>- T/M joint: Micrognathia</li> <li>- Atlantoaxial joint: subluxation</li> <li>- RF +ve type mimic adult form, with <math>\uparrow\uparrow</math> severity &amp; <math>\uparrow\uparrow</math> deformities</li> <li>- ANA is +ve in 40-85%</li> </ul>	
Uveitis may be asymptomatic	Quadriplegia	

## Differential Diagnosis

1. SOJRA Vs Leukemia (Fever pattern, site of pain, morning stiffness...)

	SOJRA	Leukemia
TLC		
Platelets		
ESR		

2. Other causes of arthritis: Rheumatic fever...

# Rickets

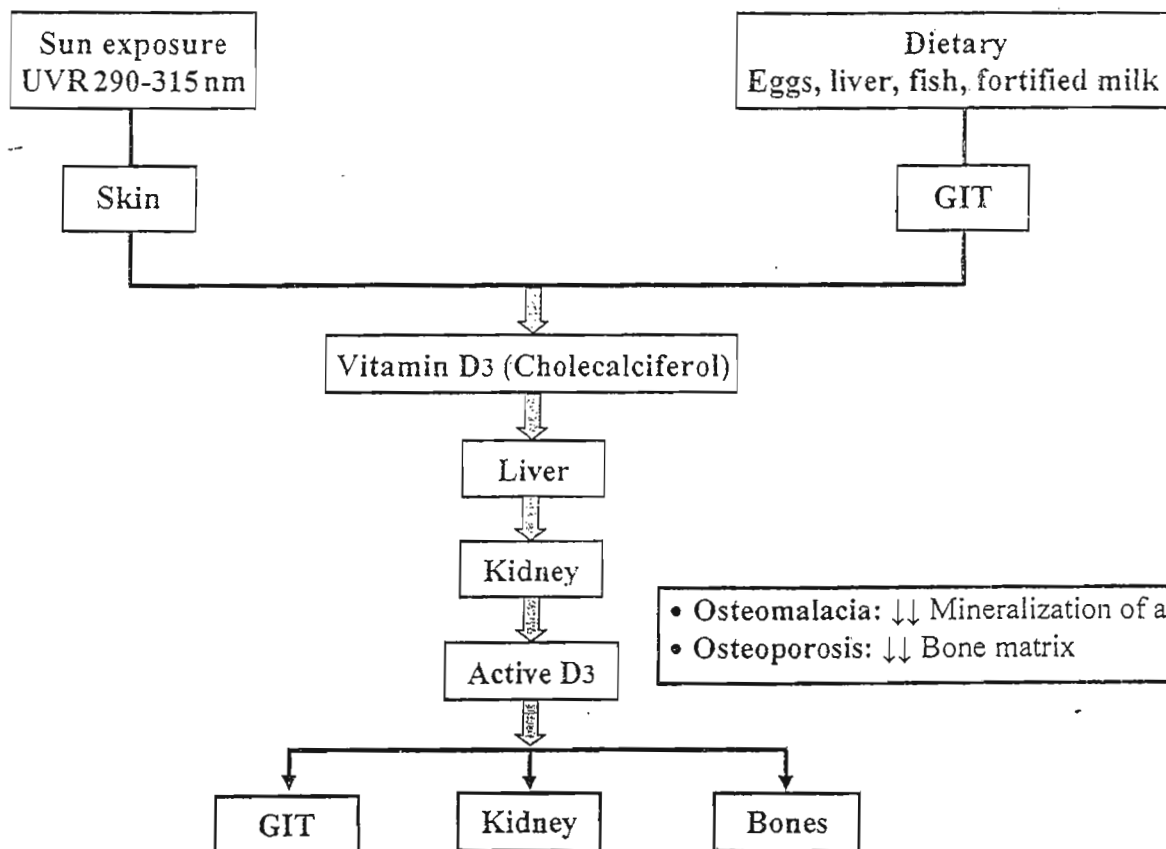
## Definition

Defective mineralization of the growing bones (Disease of childhood)

## Classification

	Vitamin D deficiency rickets	Non-Vitamin D deficiency rickets
Incidence	More common	Less common
Age	6 months-2 years	Any age
Response to Vit D Rx	Good	Poor

## Physiologic Considerations



## Hormonal Regulation of Ca Homeostasis

	Vitamin D	Parathyroid hormone
Intestine	↑↑ Ca absorption	↑↑ Ca absorption (↑↑ Vitamin D)
Kidneys	↑↑ Ca reabsorption	Phosphaturia
Bones	Normal mineralization of bones	Bone resorption (↑↑ Osteoclasts)

**Normal Bone** Matrix (Osteoid tissue) + Minerals (Ca & P)

**In Rickets:** Proliferation without degeneration

## Clinical Variants of Rickets (= Classification)

Type	Ca	PO <sub>4</sub>	ALP
<b>I. Ca deficiency with 2ry ↑ PTH</b>			
Vitamin D deficiency	Normal or ↓↓	↓↓	↑↑
Malabsorption of vitamin D	Normal or ↓↓	↓↓	↑↑
Hepatic disease	Normal or ↓↓	↓↓	↑↑
Renal osteodystrophy	Normal or ↓↓	↓↓	↑↑
Anticonvulsant drugs	Normal or ↓↓	↓↓	↑↑
Vitamin D dependent rickets type 1	↓↓	Normal or ↓↓	↑↑
<b>II. 1ry PO<sub>4</sub> deficiency (No 2ry ↑ PTH)</b>			
Hypophosphatemic rickets	Normal	↓↓	↑↑
Fanconi syndrome	Normal	↓↓	↑↑
RTA type II	Normal	↓↓	↑↑
Oncogenic hypophosphatemia	Normal	↓↓	↑↑
↓↓ Intake	Normal	↓↓	↑↑
TPN	Normal	↓↓	↑↑
<b>III. End-organ resistance to 1,25 (OH)<sub>2</sub></b>			
Vitamin D dependent rickets type 2	↓↓	Normal or ↓↓	↑↑
<b>IV. Cases resembling rickets</b>			
Hypophosphatasia	Normal	Normal	↓↓
Metaphyseal dysplasia	Normal	Normal	Normal

## Investigations

### A) Laboratory

- Serum calcium: Normal or ↓↓, When? (N = 9-11 mg/dl)
- Serum phosphorus: ↓↓ (N = 4.5-6.5 mg/dl)
- Serum alkaline phosphatase: ↑↑ (Early manifestation)

### B) Imaging (Radiological improvement start to occur after 2 wks of vitamin D Rx)

	Active	Healing	Healed
Metaphysis	Broadening Cupping Fraying	Dense <u>concave</u> white line of calcification	Dense <u>straight</u> white line of calcification
Diaphysis	↓↓ Bone density Fractures (Green-stick) Double periosteal line	Still there is manifestations of active rickets (but less severe)	Improved bone density
Epiphysis	↑↑ Joint space Bone age (Carpal bones)		

### Important Remarks:

- All cases of rickets have hypophosphatemia except...
- All cases of rickets have hyperphosphatasia except...
- 50-70 % of patients with Vitamin D dependent rickets type 2 have...
- Active form of vitamin D...
- Rx of Hypophosphatemic rickets include PO<sub>4</sub> & Vitamin D, Why???

# Rickets Sheet

## History

- Age
- Complaint: Delayed motor milestones, Chest, Teething
- Nutritional history: Breast!!
- Exposure to sun
- Hepatic symptoms
- Renal symptoms
- Drugs
- Complications: Convulsions, Fractures...
- Rx & response to Rx
- Family history

## Examination

- Vital signs: BP, Temperature, HR, RR
- Anthropometric measurements: Head circumference
- Head: Frontal bossing, Delayed closure of AF, Delayed dentition
- Limbs: Broadening, Marfan sign, Deformities
- Chest: Rosary beads, Pigeon chest, Harrison sulcus, Longitudinal sulcus
- Spine: Kyphosis, Scoliosis, Kyphoscoliosis
- Carpopedal spasm
- Chest: Infection...
- Abdomen: Hepatomegaly (Ptosed)
- Alopecia

Correctable
-------------

## Diagnosis

- A case of Nutritional rickets (Vitamin D deficiency rickets), complicated by delayed milestones & chest infections
  
- A case of Non-Nutritional rickets (Vitamin D resistant rickets), complicated by limb deformities
  
- A case of Non-Nutritional rickets (Non-Vitamin D deficiency rickets), most probably...complicated by deformities & LL fracture

## Clinical Variants of Rickets (= Classification)

Type	Ca	PO <sub>4</sub>	ALP
<b>I. Ca deficiency with 2ry ↑ PTH</b>			
Vitamin D deficiency	Normal or ↓↓	↓↓	↑↑
Malabsorption of vitamin D	Normal or ↓↓	↓↓	↑↑
Hepatic disease	Normal or ↓↓	↓↓	↑↑
Renal osteodystrophy	Normal or ↓↓	↑↑	↑↑
Anticonvulsant drugs	Normal or ↓↓	↓↓	↑↑
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Oncogenic hypophosphatemia	Normal	↓↓	↑↑
↓ Intake	Normal	↓↓	↑↑
TPN	Normal	↓↓	↑↑
<b>III. End organ resistance to 1,25-(OH)<sub>2</sub>D</b>			
Vitamin D dependent rickets type 2	↓↓	Normal or ↓↓	↑↑
<b>IV. Cases resembling rickets</b>			
Hypophosphatasia (X-linked hypophosphatasia)	Normal	Normal	↓↓
Metaphyseal dysplasia	Normal	Normal	Normal

## Investigations

### A) Laboratory

- Serum calcium: Normal or ↓↓, When? (N = 9-11 mg/dl)
- Serum phosphorus: ↓↓ (N = 4.5-6.5 mg/dl)
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Diaphysis	↓↓ Bone density Fractures (Green-stick) Double periosteal line	Still there is manifestations of active rickets (but less severe)	Improved bone density
Epiphysis	↑↑ Joint space Bone age (Carpal bones)		

• > years → most probably non-nutritional

### Important Remarks:

- All cases of rickets have hypophosphatemia except.. Renal osteodystrophy
- All cases of rickets have hyperphosphatasia except.. Cong. hypophosphatasia
- 50-70 % of patients with Vitamin D dependent rickets type 2 have alopecia
- Active form of vitamin D...
- Rx of Hypophosphatemic rickets include PO<sub>4</sub> & Vitamin D. Why??? To avoid ↑ of PTH.  
(one alpha)

# Achondroplasia

## Inheritance

- AD but > 50-80 % new mutation
- FGFR3 gene: Fibroblast growth factor receptor 3 gene on chromosome 4

## Clinical Picture

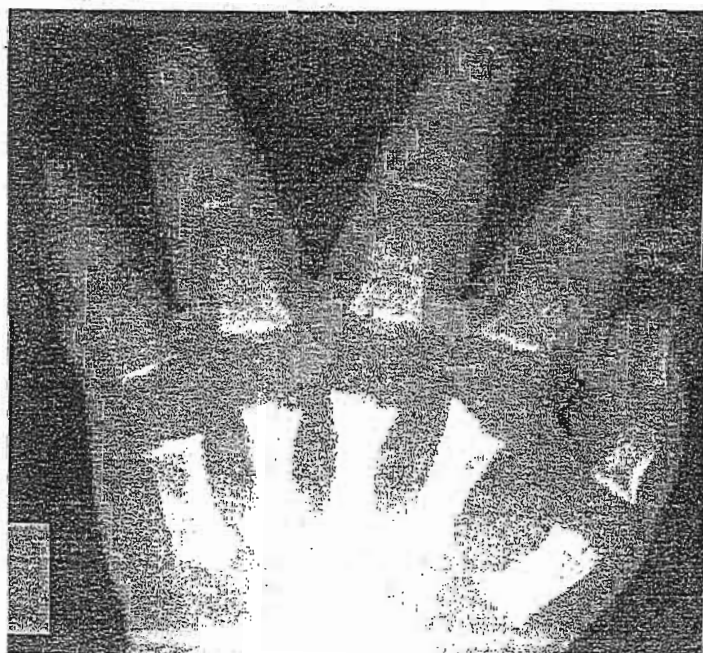
- Large head, short limbs & normal trunk
- Normal mentality
- Macrocephaly
- Short limb dwarfism (Rhizomelic)
- Prominent forehead
- Midfacial hypoplasia & depressed nasal bridge
- Trident hand
- Thoracolumbar Kyphosis

## Radiology

- Diminishing interpeduncular distance between L1 & L5
- Flaring of the ends of the long bones
- Narrow sacrosciatic notches
- Short rounded iliac bones

## Complications

- Hydrocephalus
- Spinal cord or brain stem compression
- Spinal canal stenosis
- Dental malocclusion
- Otitis media
- Sleep apnea



# Growth & Development

## Growth

- **Definition:** Increase in the size & number of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone
  - Puberty: Growth hormone & sex hormones

## Development

- **Definition:** Maturation of function & skills
- It can be assessed by evaluation of mental, motor & sexual development

## Growth Stages

### A) Intrauterine stage (= Prenatal)

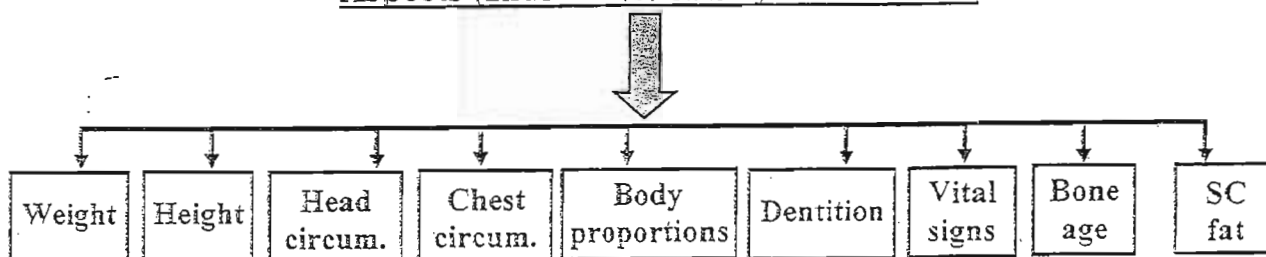
- a. Embryonic period: 1<sup>st</sup> 8 weeks
- b. Fetal period: 9-40 weeks
  - Early fetal period: 9-24 weeks
  - Late fetal period: 25-40 weeks

### B) Extrauterine stage (= Postnatal)

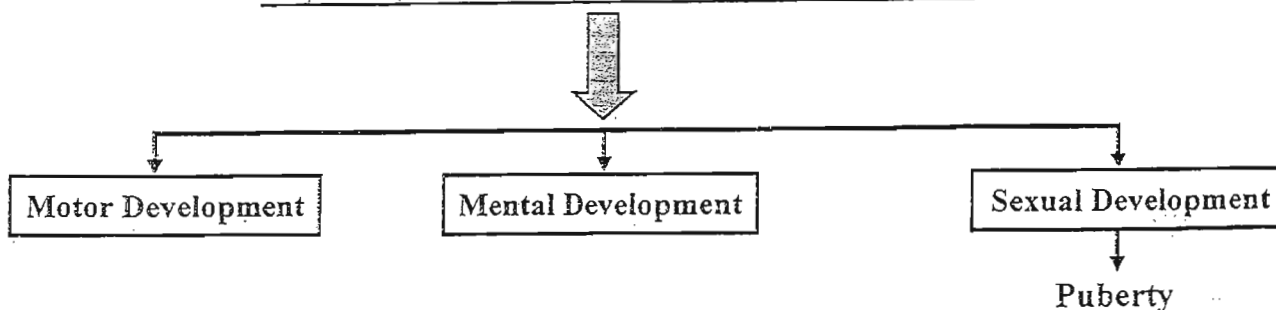
- a. Neonatal period: 1<sup>st</sup> 28 days
- b. Infancy: 1<sup>st</sup> 2 years of life (after the neonatal period)
- c. Childhood: 2 yrs-12 yrs
  - Early childhood: 2-6 yrs [Preschool years]
  - Late childhood: 6-12 yrs [School years]
- d. Adolescence: 10-20 yrs

## Normal Growth & Development

### Aspects (Indicators) of Physical Growth



### Aspects (Indicators) of Normal Development





# Normal Growth

### Weight

Age	Weight	Comment
Birth	3	
1 month	3.750	
2 months	4.500	1 <sup>st</sup> 4 months
3 months	5.250	750 g/month
4 months	6	
5 months	6.500	
6 months	7	2 <sup>nd</sup> 4 months
7 months	7.500	500 g/month
8 months	8	
9 months	8.250	
10 months	8.500	3 <sup>rd</sup> 4 months
11 months	8.750	250 g/month
12 months	9	
2 years	12	
3 years	14	
4 years	16	
5 years	18	
6 years	20	
7 years	22.5	
8 years	25	
9 years	27.5	
10 years	30	

$$Wt = (2 \times \text{age}) + 8$$

2.5 Kg/yr

### Remember

#### Weight

- Doubled at 4 months
- Tripled at 12 months
- 8 Kg at 8 months

### Height & Length

Age	Height	Comment
Birth	50	
6 month	68	25 cm/ year
1 years	75	
2 years	87	
3 years	94	
4 years	100	
5 years	107	
6 years	114	4-8 years
7 years	121	7 cm/year
8 years	128	
9 years	135	
10 years	140	9-12 years-
11 years	145	5 cm/year
12 years	150	

NB: Height (2-12 yrs)

$$\text{Height} = (6 \times \text{age}) + 77$$

### Height or Length??

- Height: Standing, in children > 2-3 yrs
- Length: Supine, in children < 2-3 yrs

### Remember

#### Height

- Doubled at 4 years
- Tripled at 12 years
- 75 cm at 1 year

### Head circumference

Age	H. Circ.	Comment
Birth	35	
6 months	43	12 cm in the 1 <sup>st</sup> year
1 year	47	
2 years	49	
6 years	51	6 cm in the next 11 years
12 years	53	

### Fontanel

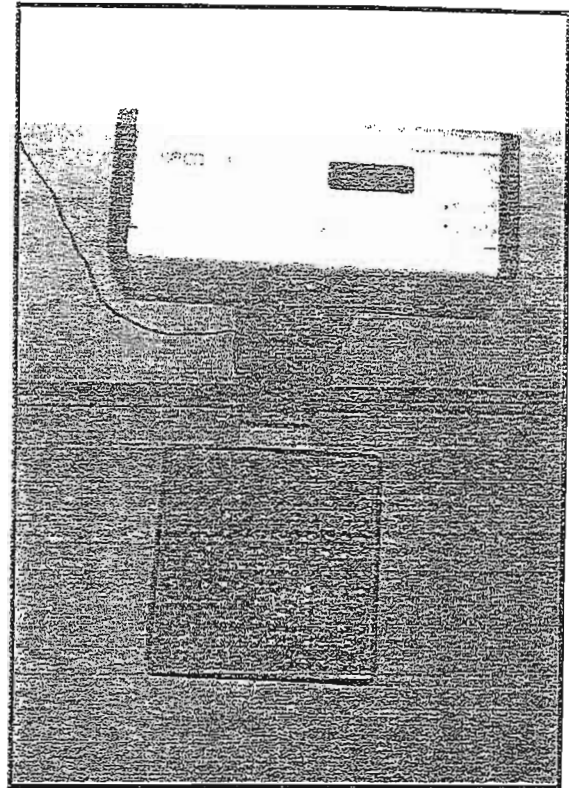
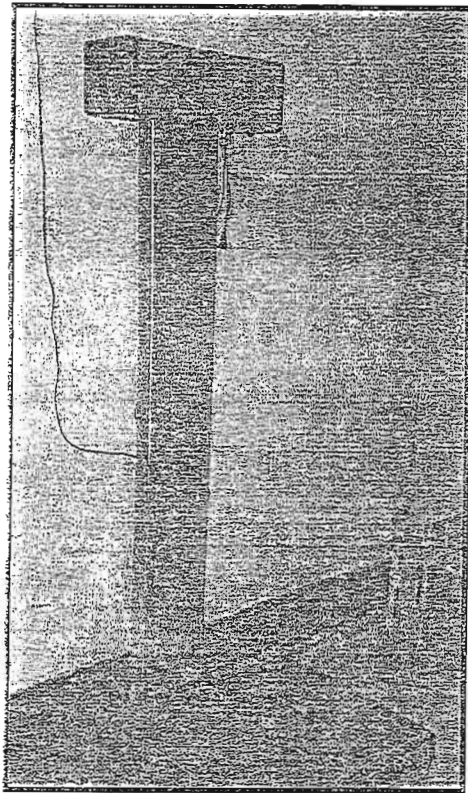
Age	Anterior	Posterior
Birth	3 fingers	Closed
6 months	2 fingers	
1 year	1 fingers	Open in Congenital Hypothyroidism
1.5 years	Closed	

### Head Circumference (Thin plastic tape)

- Anteriorly: Midway between the hairline & eyebrows
- Posteriorly: Occipital prominence

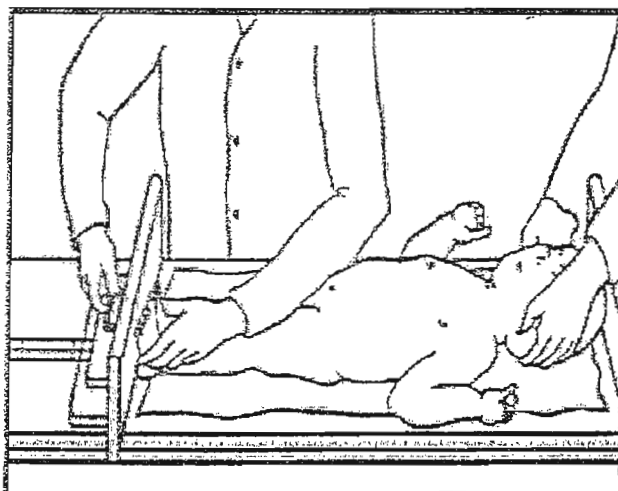
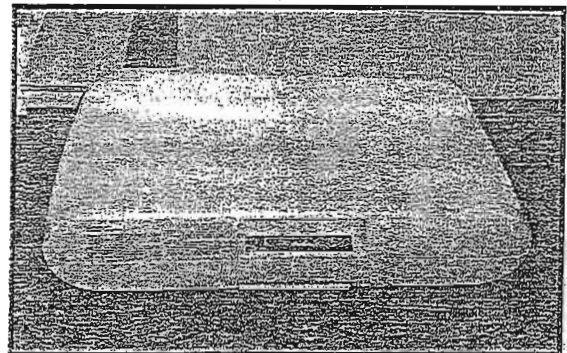


## Instruments for Weight & Height Measurement

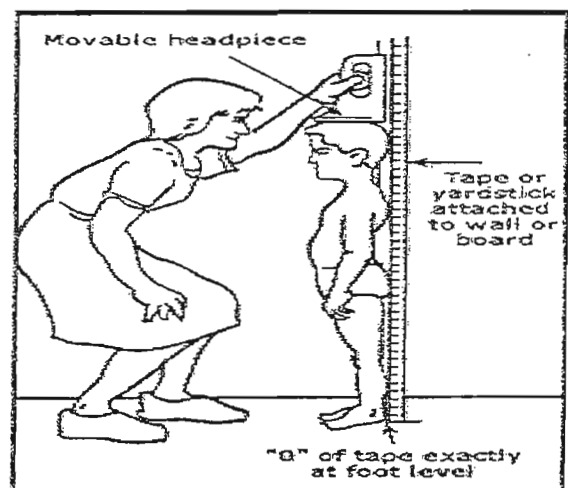


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer

Height is measured using stadiometer

## Body proportions

- ☑ **Height:** Should be measured against an appropriate vertical measure
- ☑ **Lower segment:** Measured from the upper border of the symphysis pubis to the floor
- ☑ **Upper segment:** Total height – lower segment (Top of the head & symphysis)
- ☑ **Span:** Distance between the tips of middle fingers when the arms are fully extended

### Normal US/LS ratio:

- At birth: 1.7 (Umbilicus is in the middle)
- At 3 yrs: 1.3
- At 7 yrs: 1 (Symphysis is in the middle)

### Normal Height/Span ratio:

- < 7 yrs: Span < Height
- At 7 yrs: Span = Height

## Dentition

### Primary (Deciduous) teeth

Tooth	Age (months)
Central incisor	6
Lateral incisor	9
1 <sup>st</sup> Molar	12
Canine	18
2 <sup>nd</sup> Molar	24

Teething in the lower jaw precedes the upper jaw by 1-2 months

20      32

### Secondary (Permanent) teeth

Tooth	Age (yrs)
1 <sup>st</sup> Molar	6
Central incisor	7
Lateral incisor	8
1 <sup>st</sup> Premolar	9
2 <sup>nd</sup> Premolar	10
Canine	11
2 <sup>nd</sup> Molar	12
3 <sup>rd</sup> Molar	18-24

## Vital Signs

	Heart Rate (min)	Respiratory Rate (min)	Blood Pressure
Newborn	130	60	80/60
6 months	120	50	80/60
1 year	120	40	90/60
4 years	100	25	90/60
10 years	90	20	100/65

## Chest Circumference

- At birth: Head circumference is > Chest circumference. Chest circumference = 33 cm
- At 6 months: Head circumference = Chest circumference. Chest circumference = 43 cm
- After 1 yr: Head circumference < Chest circumference
- At 5 yrs: Chest circumference = 56 cm

## Skeletal Maturation (Bone age)

- Bone age is a measure of maturation of the epiphyseal centers (ossification)
- Normally, bone age corresponds to the chronological age
- Gives an idea of potential height & clue to the cause of short stature
- Bone age is determined by radiological assessment (*Grulich-Pyle tables*)
- Reference atlases are available
- Site of assessment of bone age differ according to the age:
  - a. At birth & neonatal period: Ossific centers around the knee joint
  - b. Early childhood: Carpal bones (Roughly, one carpal bone appears/year)
  - c. Late childhood & adolescence: Fusion of epiphyses

Age	Assessment of bone age
Birth	Lower end of femur Upper end of tibia
3 months	Head of humerus
6 months	Epiphysis of radius
9 months	Head of femur
12 months	Epiphysis of tibia
2-6 years	Appearance of carpal bones <ul style="list-style-type: none"> <li>▪ 6 months: One carpal bone</li> <li>▪ 1 year: 2 carpal bones</li> <li>▪ 2 years: 3 carpal bones</li> <li>▪ 3 years: 4 carpal bones</li> <li>▪ 4 years: 5 carpal bones</li> <li>▪ 5 years: 6 carpal bones</li> <li>▪ 6 years: 7 carpal bones</li> </ul>
Later on	Time of epiphyseal fusion

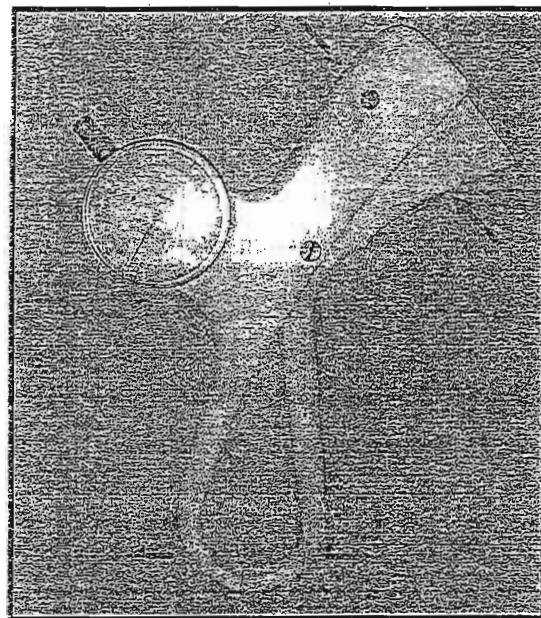
Left wrist or left knee X-ray  
are used if age < 2 yrs

## Interpretation (Variation) of Bone age

Delayed bone age	Advanced bone age
Delayed puberty	Precocious puberty
Constitutional short stature	Excessive androgen production (CAH)
Hypothyroidism	Hyperthyroidism
GH deficiency	Exogenous obesity
Severe illness	
Prematurity	
Malnutrition	

## Subcutaneous Fat Thickness

- Normal variation of fat distribution
  - First year: Excessive fat deposition
  - From 2-3 years: No more fat deposition
  - Puberty: Characteristic fat deposition in females (Buttocks & Breast)
- Site of assessment
  - Limb fat: Over the triceps
  - Trunk fat: Over ASIS
- Abnormalities of SC fat thickness
  - Increased: Obesity
  - Decreased: Malnutrition (Cachexia)
- Measured by special device ➡



# Factors affecting physical growth

## Factors affecting Intrauterine Growth

### A) Primary or Biological Factors (Inherent)

1. Maternal nutrition & general condition
2. Maternal parity: babies born to multiparous mothers tend to be larger
3. Maternal size: babies born to large mothers tend to be larger
4. Maternal age: babies born to young mothers (< 20 yrs) tend to be smaller
5. Maternal environment: babies born at high altitudes tend to be smaller
6. Genetic & constitutional factors: Fetal sex  
Male babies grow faster & are more muscular

### B) Secondary Factors

#### a. Maternal factors

##### 1. Teratoges

Definition: Teratogen is any environmental agent (drug, substance or exposure) that interferes with normal embryonic development (structure, growth or function)

##### Examples:

- Drugs: Thalidomide...
- Infection
- Maternal diseases DM & PKU
- Radiation (ionizing & non-ionizing)

##### Mechanism of teratogens:

- DNA damage
- Cell death
- Vascular insult
- Delayed differentiation

##### Mechanism of teratogens:

1. DNA damage
2. Cell death
3. Vascular insult
4. Delayed differentiation

##### 2. Congenital Infections

##### Examples:

- Rubella, Toxoplasmosis
- CMV, HSV

##### Mechanism of teratogens:

3. Severe malnutrition
4. Smoking
5. Chronic diseases: Cardiac, renal, vascular, endocrinal...
6. Pregnancy-related diseases: PIH
7. IU hypoxia
8. Placental & cord factors  
➤ Placental insufficiency

## b. Fetal factors

1. Congenital anomalies
2. Genetic or chromosomal abnormalities
3. Congenital infections
4. Multiple pregnancies
  - Till 29 wks of gestation → The same weight as singleton (of the same GA)
  - After 33 wks of gestation → The weight of each twin is less than the singleton
  - Average weight at term = 2.600 gm [average singleton = 3.200 gm]
5. Metabolic diseases

## c. Endocrinal factors

### 1. Insulin

- Insulin is an anabolic hormone (↑↑ protein synthesis)
- It is well transmitted to the fetus (Transplacental) & produced in the fetus by the 3<sup>rd</sup> month of gestation
- IDM are macrosomic due to fetal hyperinsulinemia

### 2. IGF-II

### 3. Human placental lactogen (= Human chorionic somatomammotropin)

- Placental hormone
- Its structure is similar to that of GH
- Has a growth-stimulating activity (acts as maternal GH of pregnancy!)
- Its amount is proportionate to the size of the placenta

### 4. Other hormones

- Fetal pituitary GH: No role
- Fetal thyroxine: No role
- Androgens

### Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann S
3. Cerebral gigantism (Sotos)
4. IGF-II excess

# Assessment of Growth

## Definition of Growth

- **Definition:** Increase in the size & number of cells
- It can be assessed by measurements as Weight, Height & Skull circumference

## General Features (= General Considerations)

- It is a **continuous** process
- It involves many aspects (*See before*)
- The age of development of different milestones is **variable** (= Wide normal range):
- Chronological age, physical growth & development usually evolve **hand in hand**
- Growth represents the **interaction** of heredity & environment
- It is not a **uniform** process
  - Rate: Fetal period is the fastest period of growth
  - Pattern: Head circumference increases mainly during the 1<sup>st</sup> 2 yrs of life

## Growth Curves

### Definition

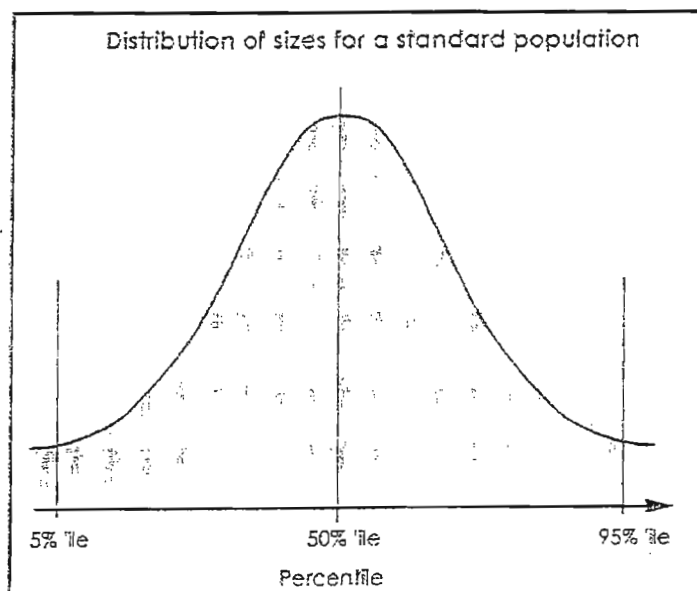
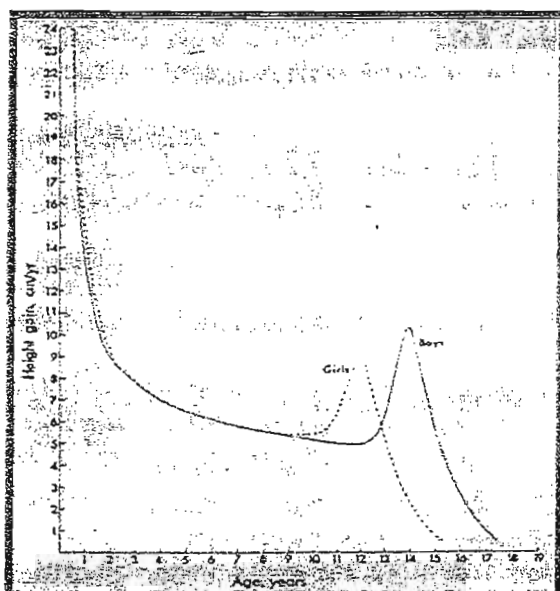
- Graphic method for assessment of physical growth
- By plotting various growth parameters against the age (e.g., Weight & height for age...)

### Rational (= Why should growth curves be used?)

- There is wide range of variation among **normal** children
- Growth curves are used to detect any **abnormal** growth pattern

### Types

- Percentile growth curves (Most commonly used)
- Velocity growth curves: Most accurate (*Rate of increase per time*)
- Standard deviation growth curves



## Velocity Growth Curves

### Definition

- Annual rate of growth velocity
- It is a measurement of gain from year to another
- It can detect any acceleration or deceleration from normal
- It is the most accurate type of growth curves (Gold standard for growth assessment)

### How to create

- Two measurements are needed 4-12 months apart
- Divide the height difference by the time interval
- The result is expressed as cm/year growth velocity

### Description of Normal Velocity Growth Curve

- Normally, Growth velocity decreases from birth afterward
- Early (up to 4-5 yrs), the deceleration is very rapid
- Then lessens in the prepubertal stage
- From the age of 3 yrs till start of puberty, difference  $> 2$  cm/yr is unusual

### Value (= Why most accurate?)

1. It reflects the child status at any particular point (This year & not all preceding years)
2. It can detect any acceleration or deceleration from normal
3. Can monitor the effect of treatment e.g., GH therapy...

NB: Criteria for stopping GH therapy:

- Growth rate  $< 1$  inch/year
- Bone age  $> 14$  yr in ♀ &  $> 16$  yr in ♂

## Percentile Growth Curves

### Definition

- Available for different aspects of growth (Weight, Height, Head circumference)
- Available for different sexes (Males & Females)
- Should be available for each country (Egyptian growth curves are now available)

### How to create

- Measure a certain parameter (e.g., height) in 100 healthy child
- Categorize them in 7 groups (*See below*)

### Description of Normal Velocity Growth Curve

- Formed of 7 percentiles:
  - 50<sup>th</sup> percentile is the average (= Median)
  - 25<sup>th</sup> percentile is below average
  - 10<sup>th</sup> percentile is low normal
  - 5<sup>th</sup> percentile is lowest normal
  - 75<sup>th</sup> percentile is above average
  - 90<sup>th</sup> percentile is high normal
  - 95<sup>th</sup> percentile is highest normal



# Factors affecting Growth

## 1. Genetic factors

- Rate of growth depends on interaction between genetic & environmental factors
- It is a polygenic inheritance
- Children inherit their height & body frame from their parents
- Familial short stature is a good example

## 2. Race

- There is racial difference in growth rate, due to:
  - Genetic factors
  - Nutritional factors
  - Climate may have an impact
- Negroes grow faster than whites
- Yellow race tend to be short
- Scandinavians tend to be tall
- Therefore, Growth curves should be available for each country
- Egyptian growth curves are now available

## 3. Age

- Fetal: Fastest period of growth (*See factors affecting IU growth*)
- Infancy: Nutrition (Substrate availability)
- Childhood: Growth hormone (& Thyroxine)
- Puberty: Sex hormones (& Growth hormone)

## 4. Sex

- Females grow faster than boys from 7 months to 4 yrs
- Females start & complete pubertal changes before males (Age of puberty in ♀ & ♂)
- Growth curves should be available for different sexes (Males & Females)

## 5. Nutrition

- Under-nutrition leads to growth failure
- Over-nutrition leads to obesity
- Episodes of malnutrition is followed by catch-up growth

## 6. Socioeconomic factors (Education, food supply, housing...)

- Low socioeconomic level → Poor hygiene, poor nutrition & poor health
- High socioeconomic level → Better growth

## 7. Season

- There is seasonal variation in growth rate
- Height growth is fastest in Spring
- Weight growth is fastest in Autumn

## 8. Diseases

- Acute short illnesses: No affection of growth (Catch-up mechanism)
- Chronic illnesses (Cardiac, hepatic, renal diseases...): Marked affection of growth

## 9. Psychological factors

- Disturbed child-mother or family relation leads to functional hypopituitarism

## 10. Secular trend

- **Definition:** Deviation of the rate of growth through successive generations provided that all other factors affecting growth are constant
- **During the last 100 yrs**, there is a striking tendency for faster growth & maturation with successive generations (Earlier menarche, increased height potential...)
- **Importance:** Index of development of a community
- **Causes of + Ve secular trend:** Better nutrition & socioeconomic development
- **Causes of - Ve secular trend:** Wars, epidemics, famines...

## 11. Endocrinal Factors

### a. Hormones with a Direct effect on growth

#### ☒ Growth Hormone

- Protein hormone secreted by the anterior pituitary gland
- Pulsatile secretion more with sleep
- Action is mediated by insulin like growth factor-1 (*IGF-1*) or "Somatomedin C" formed by the liver
- Action:
  - **Growth:** ↑↑ Size of various tissues (bones, cartilage, muscles & viscera).
  - **Proteins:** Anabolic.
  - **CHO:** ↑↑ Gluconeogenesis.
  - **Lipids:** ↑↑ Lipolysis.
  - **Electrolytes:** ↑↑ Ca, ↑↑ Na, ↑↑ PO<sub>4</sub>

#### ☒ Thyroid Hormone

- Protein hormone secreted by the thyroid gland
- Action is mediated by insulin like growth factor-1 (*IGF-1*) or "Somatomedin C" formed by the liver
- Action:
  - Calorigenic
  - Protein: Anabolic in physiologic dose, catabolic in large dose
  - **Growth:** Necessary for GH & IGF-1 synthesis & action
  - Bone: ↑↑ Bone age
  - CNS: Important for the rapidly growing brain (synapses, myelination)
  - Sexual maturation: Delayed in hypothyroidism (? precocious puberty...)

#### ☒ Sex Steroids

- Steroid hormones
- ↑↑ Bone age
- Concerned mainly with pubertal growth spurt
- Important for the development of 2ry sex characters
- Testosterone is important for virilization of the male fetus (CAH in a ♀...)

### b. Hormones with an Indirect effect on growth

#### ☒ Insulin

- Protein hormone secreted by the pancreas
- Anabolic hormone
- Has a growth-promoting effect through interaction with GH & IGF-1

#### ☒ Glucocorticoids

- Steroid hormone secreted by the adrenal gland
- Required in physiological amount for optimum growth
- **Excessive amount:** Direct inhibition of epiphyses, ↓↓ GH, ↓↓ IGF-1



### Normal child on percentile growth curves should:

- Lie between the 5<sup>th</sup> & 95<sup>th</sup> percentiles
- Follow his own percentile (Marked deviation should be investigated)
- All the growth parameters should follow the same percentile level

### Abnormalities in percentile growth curves

- Values < 5<sup>th</sup> % are abnormal
- Values > 95<sup>th</sup> % are abnormal
- Sustained deviation from the child own percentile is abnormal

### Value & Importance

- Demonstration of **normal** growth pattern (Each child has his own pattern of growth)
- Educational demonstration
- Summary of growth data over a long period
- Statistical value
- Diagnosis of abnormal growth:
  - **Single measurement:** Values < 5<sup>th</sup> % or > 95<sup>th</sup> % are abnormal
  - **Serial measurements:** Sustained deviation from the child own percentile is abnormal
- A single growth parameter should not be assessed in isolation from other growth parameters; e.g., a child's weight may be normal in proportion to his height if he is short, but low weight if tall [**Weigh for height curves are available**]
- **Weigh for height** < 5<sup>th</sup> percentile is the **single** best indicator of acute undernutrition
- **Catch-up growth:** Period of accelerated growth following a period of growth arrest
- Can monitor the effect of treatment e.g., GH therapy...
- Demonstration of drug side effects on growth e.g., steroids in SLE...
- Prediction of adult height

### Errors in Interpretation of Growth Curves

- Obesity: Excess fat
- Kwashiorkor: Edema
- Interpretation of growth curves should be done together with proper clinical examination

### **Catch-up Growth**

**Definition:** Period of accelerated growth following a period of growth arrest or restriction

**Importance:** Allows child to attain his target centile of growth

**Types:** Complete or incomplete

**Examples:**

- Gastroenteritis
- PEM
- GIT surgery (Atresia, CHPS...)

**Factors affecting catch-up:**

- **Onset:** The earlier, the more difficult to achieve a complete catch-up
- **Duration:** The longer the duration of the stress, the more difficult to achieve a complete catch-up
- **Sex:** Females show a more complete catch-up than males

### Weight-for-Age Percentiles: Egyptian Boys, Birth to 36 Months



# Developmental Milestones

## Definition of Development

- Definition: Maturation of function & skills
- It is due to: Functional maturation & myelination of the CNS

## General Features (= General Considerations)

- It is a continuous process
- Chronological age, physical growth & development usually evolve **hand in hand**
- Motor development occurs in a **cephalocaudal** & **central-to-peripheral** direction:  
Truncal control → Arm control → Finger control
- Motor development is related to **brain development**. So, motor development is affected in children with MR
- Development represents the **interaction** of heredity & environment on the brain
- Environment provides physical & psychological needs:
  - Physical: Food, good health...
  - Psychological: Care, experiences...
- The age of development of different milestones is **variable** (= Wide normal range):
  - Median age: The age by which 1/2 standard population achieve a certain skill
  - Limit age: The age by which a certain skill should be achieved

Limit age is more useful as a guide to normal development than median age

### Example: Walking unsupported

- Median age of walking unsupported is 12 months
- Limit age of walking unsupported is 18 months

## Monitoring of Development

- a. Parents
- b. Regular child health surveillance checks
- c. Health care professional

## Developmental Milestone (= Fields of Development)

### A) Gross Motor

- Using large groups of muscle
- Examples: Sitting, standing, walking...

### B) Fine Motor (& Vision)

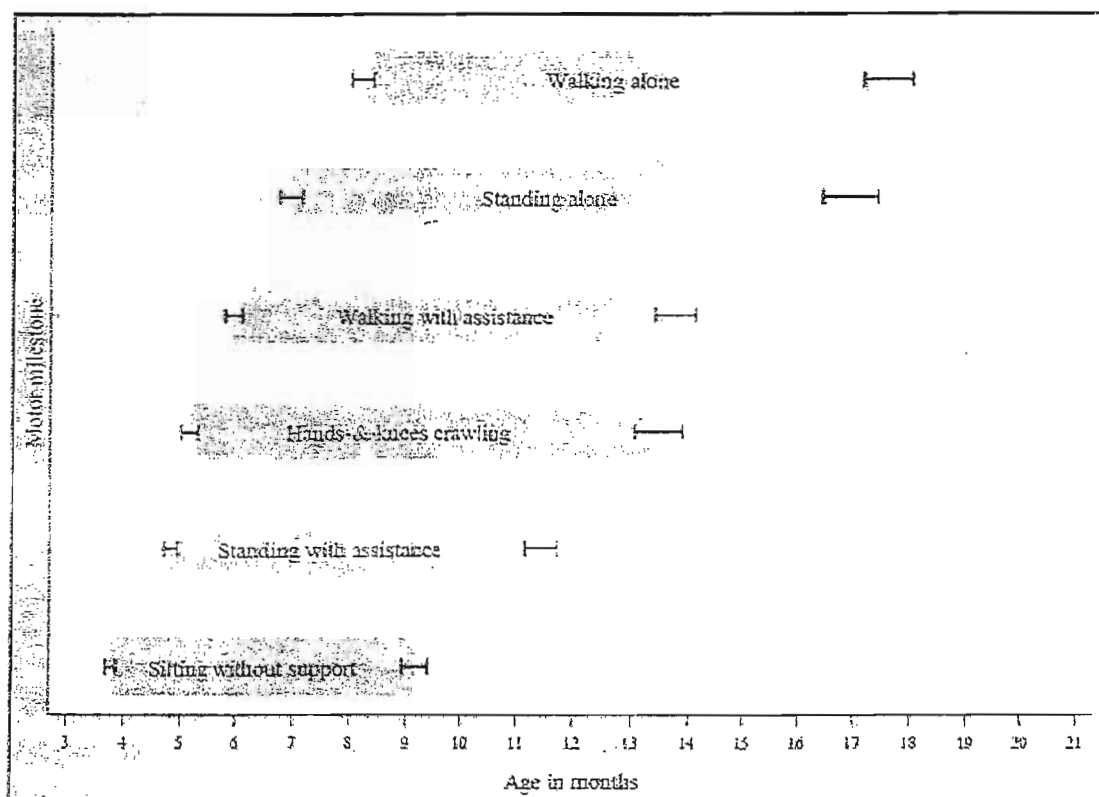
- Using hands to do fine movements
- Examples: Eating, drawing, writing, dressing...

### C) Hearing, Speech & Language

### D) Social, Emotional & Behavioral

# Gross Motor

Age	Gross Motor Development (Median Ages)
Newborn	Turns head from side to side
2 months	Raises head to 45°C
3 months	Head support Lifts head & chest (on prone position)
4 months	Pushes with feet
5 months	Sitting with trunkal support
6 months	Sitting with pelvic support
7 months	Sitting without support (1 <sup>st</sup> with round back then with straight back)
8 months	Turns from supine to prone (& reverse)
9 months	Creeping or Crawling
10 months	Standing
12 months	Walking (furniture)
15 months	Walking (alone)
1 ½ years	Ascends stairs (Child manner)
2 years	Descends stairs (Child manner) Kicks aball
3 years	Ascends stairs (Adult manner) Pedal tricycle
4 years	Descends stairs (Adult manner)
5 years	Can hop on one foot



# Precocious Puberty

## Definition

The appearance of 2ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂

	True Precocious Puberty	Precocious Pseudopuberty
Synonyms	Central (intra-cranial) Gonadotropin dependent	Peripheral (extra-cranial) Gonadotropin independent
H-H-G	Active	Inactive
FSH & LH	↑↑	↓↓
Gonads	Active	Inactive
Gametogenesis	Present	Absent
2ry sex characters	Isosexual	Isosexual or heterosexual
GnRH stimulation	↑↑ LH & FSH	No ↑↑ LH & FSH

Precocious pseudopuberty → ↑↑ bone age → activation of HHG axis → True Precocious puberty (Combined Gonadotropin dependent & Gonadotropin independent Puberty)

## Etiology

### I) True Precocious Puberty:

- Idiopathic (constitutional, functional)
- Organic brain lesions
  - Hypothalamic hamartoma
  - Intracranial lesions
  - Pineal region tumors
- Radiotherapy
- Hypothyroidism

### True precocious puberty:

- ♀ → 80% of cases are idiopathic  
♂ → 80% of cases are pathologic

### II) Precocious Pseudopuberty:

		Gonadal	Adrenal	Exogenous
Female	Isosexual (Feminizing)	<ul style="list-style-type: none"> <li>McCune-Albright S</li> <li>Autonomous ovarian cyst</li> <li>Ovarian tumors                             <ul style="list-style-type: none"> <li>Granulosa cell tumor</li> <li>Teratoma</li> </ul> </li> </ul>	Feminizing adrenal tumor	Estrogens
	Heterosexual (Virilizing)	<ul style="list-style-type: none"> <li>Ovarian tumors e.g., Androblastoma</li> </ul>	<ul style="list-style-type: none"> <li>Virilizing adrenal tumor</li> <li>CAH</li> </ul>	Androgens
Male	Isosexual (Virilizing)	<ul style="list-style-type: none"> <li>Leydig cell tumor</li> <li>Familial male precocious P.</li> </ul>	<ul style="list-style-type: none"> <li>Virilizing adrenal tumor</li> <li>CAH</li> </ul>	Androgens
	Heterosexual (Feminizing)	<ul style="list-style-type: none"> <li>Sertoli cell tumor</li> </ul>	Feminizing adrenal tumors	Estrogens

In ♂, hCG secreting tumors (Hepatoblastoma, CNS, mediastinum) → Isosexual precocious pseudopuberty

### III) Incomplete Precocious Puberty:

- Premature thelarche
- Premature adrenarche
- Premature menarche

### IV) Combined Puberty:

- Congenital adrenal hyperplasia
- McCune-Albright S
- Familial male precocious puberty

# True Precocious Puberty

**Leoprolide:** synthetic long-acting GnRH agonist  
 ▪ **Pulsatile** GnRH is needed to ↑↑ FSH & LH  
 ▪ **Continuous** GnRH stimulation: suppression

Idiopathic (Constitutional, functional)	Organic Brain lesion	PP following Radiotherapy
<p><b>Incidence</b> (♀: ♂ = 5-10:1)                      It is the cause of PP in 90% of ♀                      It is the cause of PP in <u>only</u> 25- 75% of ♂</p> <p><b>Etiology</b>                      Sporadic (?? Familial)</p> <p><b>Clinical picture</b> (<i>Synchronous as normal</i>)</p> <p>☒ <b>Females:</b>                      Breast enlargement → Pubic hair →                      Axillary hair → Menarche (+2ry sex characters)</p> <p>☒ <b>Males:</b>                      Testicular ↑↑ → Thinning &amp; pigmentation of the scrotum → Penis ↑↑ → Pubic hair                      → Axillary hair (+2ry sex characters)</p> <p>☒ <b>Both ♀ &amp; ♂:</b>                      Tall as children, Short as adults                      Gametogenesis: present (Pregnancy &amp; N.emissions)                      Mentality: compatible with chronologic age</p> <p>☒ <b>Course:</b>                      Progressive (rapidly or slowly) or regressive</p> <p><b>Investigations</b></p> <ol style="list-style-type: none"> <li><b>Gonadotropins (FSH &amp; LH)</b> <ul style="list-style-type: none"> <li>↑↑ FSH &amp; LH with detected pulsatile LH</li> <li>GnRH stimulation: Brisk response ↑↑</li> </ul> </li> <li><b>Sex hormones:</b> ↑↑ (consistent with bone age)</li> <li><b>Bone age:</b> Advanced bone age</li> <li><b>CT, MRI brain:</b> to exclude I.C. lesions (♂)*</li> <li><b>Pelvic U/S:</b> ↑↑ Ovaries, uterus ± ovarian cysts</li> </ol> <p><b>Treatment</b>                      GnRH analog (<i>Leoprolide</i>): 0.25-0.3 mg/Kg IM every 4 wks (Other routes = intra nasal, SC)  <i>Side effects:</i> Recurrent sterile fluid collection at injection sites  <i>Effects:</i> ↓↓ GTH &amp; sex hormones + ↓↓ growth rate to normal + ↑↑ adult height                      Regression of 2<sup>nd</sup> sex characters (breasts, pubic hair)</p>	<p><b>Incidence</b>                      It is the cause of PP in 10% of ♀                      It is the cause of PP in 25- 75% of ♂</p> <p><b>Etiology</b>                      1. Hypothalamic hamartoma                      2. Intracranial lesions (involving the hypothalamus)</p> <p>☒ TB meningitis                      ☒ Encephalitis                      ☒ Tumors (astrocytoma, ependymoma...)                      ☒ Trauma                      ☒ Tuber sclerosis                      ☒ Neurofibromatosis (optic glioma)</p> <ol style="list-style-type: none"> <li><b>Pineal region tumors</b> (germinoma, astrocytoma)</li> </ol> <p><b>Clinical picture</b>                      ☒ <b>Endocrinal:</b> may precede the IC lesion                      ☒ <b>Picture of the cause:</b> ↑↑ ICT, visual field...                      ☒ <b>Hypothalamic syndrome:</b> <ul style="list-style-type: none"> <li>Hypothermia, hyperthermia, adipsia, DI</li> <li>Obesity, cachexia</li> <li>Hypersomnia</li> <li>Gelastic seizures (unnatural laughing)</li> </ul> <p><b>Investigations</b> as in constitutional precocious P.  <b>Treatment</b> GnRH analog (<i>Leoprolide</i>)                      Rx of the cause</p> </p>	<p><b>Mechanism</b>                      Radiotherapy → True Precocious Puberty</p> <p><b>Clinical picture</b>                      1. Precocious puberty: ↑↑ growth                      2. GH &amp; TSH deficiency: ↓↓ growth                      3. <b>Net result:</b> Normal growth</p> <p><b>Treatment</b>                      ▪ GnRH analog (<i>Leoprolide</i>): 0.25-0.3mg/Kg IM every 4 wks                      ▪ GH &amp; Thyroid supplementation</p> <p><b>Hypothyroidism &amp; precocious puberty</b></p> <p><b>Incidence</b>                      Hypothyroidism usually cause delayed puberty*                      Precocious puberty may occur in <u>severe, untreated</u> 1ry hypothyroidism of <u>long duration</u></p> <p><b>Mechanism &amp; C/P</b>                      FSH &amp; GTH (LH &amp; FSH) have identical α-chain                      ↓↓ T<sub>3</sub>, T<sub>4</sub> → ↑↑ TSH → ↑↑ FSH receptors →                      ☒ <b>Females:</b>                      ↑↑ Estrogen → ↑↑ Breast &amp; Bleeding (menses)                      No ovulation                      ☒ <b>Males:</b>                      ↑↑ Sertoli cells → ↑↑ Testicular size                      No ↑↑ of Leydig cells → No ↑↑ testosterone                      No virilization</p> <p><b>Investigations</b>                      1. TSH &amp; prolactin: ↑↑                      2. Gonadotropins (FSH &amp; LH): ↓↓                      3. CT, MRI brain: ↑↑ Sella                      4. Pelvic U/S: Ovarian cysts</p> <p><b>Treatment</b> Thyroid supplementation (↓↓ TSH)</p>



# Precocious Pseudopuberty

Gonadotropin-Secreting Tumors	Familial male Precocious Puberty 1 <sup>st</sup> Leydig cell hyperplasia	McCune-Albright Syndrome
<p>I) <u>Hepatoblastoma</u>:</p> <p><u>Mechanism</u></p> <ul style="list-style-type: none"> <li>It secretes hCG → ↑↑ LH receptors → ↑↑ Leydig cells → ↑↑ Testosterone</li> <li>No spermatogenesis</li> </ul> <p><u>Clinical picture</u> (Only in ♂ ≈ 2 yrs)</p> <ul style="list-style-type: none"> <li>Isosexual precocious pseudopuberty</li> <li>Hepatomegaly</li> </ul> <p><u>Investigations</u></p> <ul style="list-style-type: none"> <li>hCG &amp; α-fetoprotein: ↑↑</li> <li>Plasma testosterone: ↑↑</li> <li>Gonadotropins (FSH &amp; LH): ↓↓ [In the past, ↑↑ LH due to cross reactivity with hCG]</li> <li>Testicular biopsy: Leydig cell hyperplasia</li> <li>Bone age: Advanced bone age</li> </ul> <p>II) <u>Other tumors</u>:</p> <ul style="list-style-type: none"> <li>Type: Teratoma, teratocarcinoma</li> <li>Site: CNS, mediastinum, gonads</li> </ul>	<p><u>Etiology</u> (AD)</p> <p><u>Mechanism</u> (Gonadotropin-independent)</p> <ul style="list-style-type: none"> <li>Activation mutation of LH receptors → ↑↑ Leydig cells → ↑↑ testosterone → ↑↑ bone age</li> <li>No spermatogenesis</li> </ul> <p><u>Clinical picture</u> (Only in ♂, 2 yrs)</p> <ul style="list-style-type: none"> <li>Isosexual precocious pseudopuberty</li> <li>True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined)</li> </ul> <p><u>Investigations</u></p> <ul style="list-style-type: none"> <li>Plasma testosterone: ↑↑</li> <li>Gonadotropins (FSH &amp; LH): ↓↓</li> <li>Testicular biopsy: Leydig cell hyperplasia</li> <li>Bone age: Advanced bone age</li> </ul> <p><u>Treatment</u></p> <ul style="list-style-type: none"> <li>Ketokonazole (# Testosterone synthesis)</li> <li>GnRH analog (Leuprolide): in true puberty</li> </ul>	<p><u>Etiology</u></p> <p>Autonomous hyperfunction of glands</p> <p><u>Clinical picture</u> (Usually in ♀ ≈ 3 yrs)</p> <p>I) <u>Skin</u>: Pigmentation (Café-au-lait patches)</p> <p>II) <u>Skeletal</u>: Fibrous dysplasia</p> <p>III) <u>Endocrinal</u>:</p> <ol style="list-style-type: none"> <li>Gonads → Precocious pseudopuberty [Functioning follicular cyst → ↑↑ Estrogen] True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined)</li> <li>Thyroid → Hyperthyroidism</li> <li>Adrenal → Cushing syndrome</li> <li>Pituitary → GH excess (gigantism or acromegaly)</li> </ol> <p><u>Treatment</u></p> <p>☑ <u>Functioning ovarian cyst</u>:</p> <ul style="list-style-type: none"> <li>Surgery or aspiration</li> <li>Aromatase inhibitor (<i>Testolactone</i>)</li> <li>Anti-estrogen (<i>Tamoxifen</i>)</li> <li>GnRH analog (Leuprolide): (When??)</li> </ul> <p>☑ Hyperthyroidism</p> <p>☑ Cushing</p> <p>☑ GH excess: <i>Octreotide</i></p>

# Incomplete Precocious Puberty (Partial)

## Definition

Isolated precocity of one of the 2 ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂ without development of other signs of puberty. It is usually transient

Premature Thelarche	Premature Pubarche (Adrenarche)	Premature Menarche
<p><u>Definition</u> Isolated breast development</p> <p><u>Etiology</u> Sporadic (? Familial)</p> <p><u>Clinical picture</u> ▪ Age of onset: During the 1<sup>st</sup> 2 yrs. May at birth ▪ Course: Transient (3-5 yrs) Rarely progressive ▪ Bilateral or unilateral ▪ Atypical (exaggerated) thelarche ↑↑ bone age, U/S → ↑↑ Ovaries</p> <p><u>Investigations</u> ▪ FSH, LH, Estrogen: Normal ▪ Bone age: ± Advanced bone age ▪ Pelvic U/S: ± Ovarian cysts</p> <p><u>Treatment</u> Benign but F/U is needed as it may be 1<sup>st</sup> sign of precocious puberty</p>	<p><u>Definition</u> Isolated appearance of sexual hair</p> <p><u>Etiology</u> Premature ↑↑ adrenal androgens</p> <p><u>Clinical picture</u> (♀ &gt; ♂) ▪ Sexual hair: pubic &amp; axillary hair ▪ Atypical premature adrenarche: Systemic androgenic effects (acne, ↑↑ bone age...) ▪ Course: Transient</p> <p><u>Investigations</u> ▪ FSH, LH, sex hormones: Normal ▪ DHEA: ↑↑ ▪ Bone age: ± Advanced bone age</p> <p><u>Treatment</u> Benign but F/U is needed as it may be 1<sup>st</sup> sign of precocious puberty</p>	<p><u>Definition</u> Isolated menses</p> <p><u>Clinical picture</u> ▪ 1-3 attacks of menstrual bleeding ▪ Course: Transient</p> <p><u>Investigations</u> ▪ FSH, LH, Estrogen: Normal ▪ Pelvic U/S: ± Ovarian cysts</p> <p><u>Treatment</u> Benign but F/U ...</p> <p><u>DD</u> (Vaginal bleeding) 1. Child abuse 2. FB 3. Vulvo-vaginitis 4. Uterine sarcoma</p>

## Precocious puberty in ♂:

- A) True precocious puberty
- B) Precocious pseudopuberty
  1. Isosexual
    - Gonadal: Leydig cell tumor, familial male precocious puberty
    - Adrenal: Virilizing adrenal tumor & CAH
    - Exogenous: Androgen
    - Gonadotropin-secreting tumors
  2. Heterosexual
    - Gonadal: Sertoli-cell tumor
    - Adrenal: Feminizing adrenal tumor
    - Exogenous: Estrogen
- C) Incomplete Precocious puberty  
Premature adrenarche
- D) Combined Precocious puberty
  - Familial male precocious puberty
  - CAH

## Precocious puberty in ♀:

- A) True precocious puberty
- B) Precocious pseudopuberty
  1. Isosexual
    - Gonadal: McCune-Albright \$
    - Autonomous ovarian cyst, ovarian tumors
    - Adrenal: Feminizing adrenal tumor
    - Exogenous: Estrogen
  2. Heterosexual
    - Gonadal: ovarian tumors
    - Adrenal: Virilizing adrenal tumor & CAH
    - Exogenous: Androgen
- C) Incomplete Precocious puberty  
Premature thelarche, Adrenarche, menarche
- D) Combined Precocious puberty
  - McCune-Albright \$
  - CAH

## Fine Motor

Age	Fine Motor Development & Vision (Median Ages)
Newborn	Follows light & face in midline
1 month	Follows moving objects or light
4 months	Reaches out for objects
5 months	Sitting with trunkal support
6 months	Palmar grasp (Use of the whole hand to grasp objects)
7 months	Transfers objects from one hand to another
10 months	Pincer grasp (Use of the index & thumb to grasp objects)
12 months	Waves bye-bye
18 months	Builds tower of 3 cubes Scribbles
2 years	Builds tower of 6 cubes Draws a line
2½ years	Builds tower of 8 cubes
3 years	Bridge of 3 cubes Draws a circle
4 years	Makes steps by cubes Draws a cross
5 years	Draws a triangle
6 years	Draws a man with all features "Draw-A-man test"

## Hearing, Speech & Language

Age	Hearing, Speech & Language (Median Ages)
Newborn	Cries Startle to loud noises
1 month	Follows moving objects or light
4 months	Laughs out loud Vocalization
5 months	Sitting with trunkal support
6 months	Babbling
9 months	Says Mama & Dada Mama & Dada (Specific to parents at 10-12 months)
12 months	Says 2-3 words (other than Mama & Dada)
18 months	Says 10 words Shows 2 parts of the body (Nose, ear...)
2 years	Says 3-word sentence (telegraphic)
3 years	Can tell <u>name</u> , <u>age</u> & <u>sex</u>
4 years	Counts up to 10 Recognizes 8 colors
5 years	Clear speech

## Social, Emotional & Behavioral Development

Age	Social, Emotional & Behavioral Development (Median Ages)
Newborn	Follows face in midline
2 month	Social smile
3 months	Listens to music
4-6 months	Recognition of the mother
6 months	Puts food in mouth Prefers the mother
10 months	Respond to sound of name
12 months	Waves bye-bye Mimics Drinks from a cup with 2 hands
18 months	Symbolic play Feeds with spoon
2 years	Undresses
3 years	Has friends & interactive play <i>"Takes turn in play"</i>
4 years	Dressing

## Vision Development

Age	Vision Development (Median Ages)
Newborn	Follows face in midline
2 month	Optokinetic nystagmus.
7 months	Colored vision

## Hearing Development

Age	Vision Development (Median Ages)
Newborn	Startle to loud noise
4 month	Smiles to your voice (Or quietens)
7 months	Turns towards quiet sounds
10 months	Respond to sound of name & other familiar words (No, bye-bye...)

# Primitive Neonatal Reflexes

## Definition

- Group of reflexes mediated at the subcortical level as the cerebral cortex is still functionally deficient
- With maturation of the cerebral cortex, these reflexes gradually disappear ( $\approx 4-6$  ms)
- Moro reflex is the most important because it is reliable & easy to be elicited

## Significance

- Normal neonatal reflexes indicate Normal neurological condition
- Asymmetrical response indicate Focal neurological deficit
- Persistence of these primitive reflexes indicate Cortical damage

## Moro Reflex

### Stimulus

- Sudden fall of supported head
- Sudden withdrawal of blanket
- Loud noise

### Response

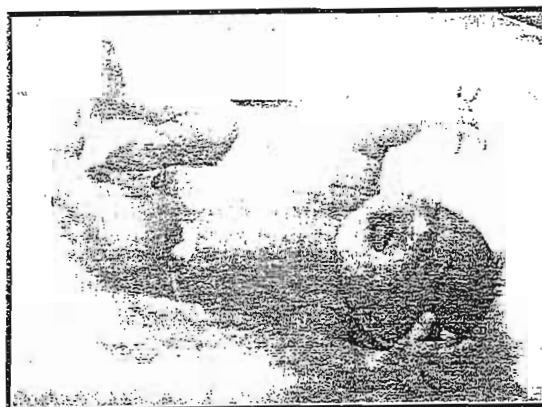
Abduction & extension followed by adduction & flexion

### Timing

- Appearance: After 27 wks of gestation
- Disappearance: At the age of 4 months

### Significance

- a. Normal response Normal CNS
- b. Absent Moro reflex (Serious)
  - Marked prematurity ( $< 27$  wks gestation)
  - Intracranial hemorrhage (ICH)
  - Asphyxia
  - CNS depression (Maternal anesthesia or  $MgSO_4$ )
- c. Asymmetrical response
  - Fracture clavicle
  - Erb's palsy
- d. Persistent Moro  $> 4-6$  months
  - Cerebral palsy
  - Mental retardation
- e. Exaggerated Moro
  - CNS irritation e.g., Kericterus



## Primitive Neonatal Reflexes

Reflex	Stimulus	Response	Time of appearance	Time of disappearance
Placing reflex	Holding the baby with the dorsum of his feet touching the undersurface of the table	Foot elevation + Placement over the table	34	1.5 months
Stepping reflex	Holding the baby with his feet touching the table	Foot elevation + Walking movement	34	1.5 months
Rooting reflex	Touching the lips or the corners of the mouth	Opening of the mouth & Head turning towards the side of stimulus	27	4 months
Suckling reflex	Stimulation of the oral cavity (Nipple or finger)	Suckling movements	27	4 months
Plantar reflex	Scratching of the outer aspect of the sole of the foot	Dorsiflexion of the big toe $\pm$ Fanning of other toes	34	1 year
Landau reflex	Holding the baby prone in a horizontal position	The body forms a convex arc + Flexion of the head, trunk & hips		
Palmar Grasp reflex	Putting a object in the palm of the hand	Flexion of the fingers & Grasping	27	4 months
Plantar Grasp reflex	Putting an object against the sole of the foot	Flexion of the toes & Grasping	27	8 months
Tonic neck reflex	Turning of the head to one side	Extension of the arm & leg on the same side + Flexion of the opposite side	34	5 months
Moro reflex	See before		27	4 months
Extrusion	Uses tongue to push foreign objects out of mouth		At birth	3 to 4 months
Parachute (forward) reflex	Holding in a position where he is dropped forward	Outstretching of the hands (Protection)	9 months of	Persists
Moro reflex	See before		27	4 months

## Primitive Neonatal Reflexes



Placing reflex



Stepping reflex



Tonic neck reflex



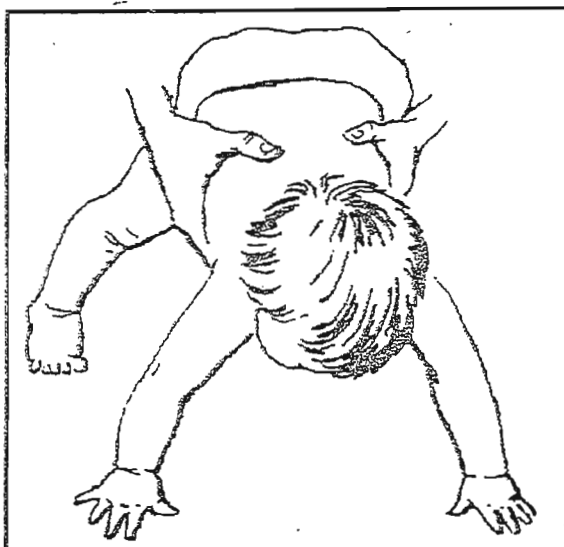
Palmar Grasp reflex



Plantar Grasp reflex



Rooting reflex



Parachute reflex



Moro reflex

## Delayed walking

### Introduction

Walking requires 3 factors:

- ☒ CNS
- ☒ Musculoskeletal system
- ☒ Training

### Etiology

#### A) Neurological causes [Central & peripheral]

- Cerebral palsy
- Mental retardation
- Hydrocephalus
- Neuromuscular disorders
  - AHC: Werdnig-Hoffmann disease & Poliomyelitis
  - Nerve: Neuropathy (e.g., Guillain-Barré syndrome...)
  - Neuromuscular junction: Myasthenia gravis
  - Muscle: Myopathy

#### B) Bone: Rickets, trauma, fractures

#### C) Training: diagnosed by exclusion

## Delayed Sphincteric Control

### Etiology

1. Neurological causes: Mental retardation...
2. Maturation delay
3. Mismanagement
4. Lack of training
5. Emotional

## Delayed Speech

### Etiology

1. Neurological causes: Mental retardation...
2. Familial
3. Deafness:
  - ☒ Conductive: OM, Eustachian tube dysfunction (Cleft palate), Wax...
  - ☒ Sensorineural: Genetic, Alport, HIE, Kernicterus, Meningitis, Trauma, drugs (aminoglycosides, frusemide...), Neurodegenerative diseases
4. Emotional
5. Lack of training
6. Autism



# Assessment of Gestational Age

## Importance

- a. Proper assessment of fetal growth, fetal well being & fetal functional maturity
- b. Proper timing of antenatal diagnostic procedures (amniocentesis & CVS)
- c. Proper timing of elective obstetric procedures (elective CS)
- d. Identification of premature delivery (? neonatal management)

## Methods

- a. History: 1<sup>st</sup> day of the last menstrual period (LMP)
- b. Examination: Fundal level
- c. U/S
  - 1<sup>st</sup> trimester: Crown-rump length
  - 2<sup>nd</sup> trimester: Biparietal diameter & femur length
- d. Neonatal reflexes
- e. New Ballard score
  - Neuro-muscular maturation
  - Physical maturation
- f. Laboratory & Radiological investigations
  - Ig
  - EMG, EEG, X ray
  - AF maturation, how?
  - Fetal Hb%

Neuro-muscular maturity	Physical maturity
Posture	Skin
Square window	Lanugo
Arm recoil	Plantar creases
Scarf sign	Breast
Polpliteal angle	Eye/ear
Heel to ear	Genitalia (♂ & ♀)

# Assessment of gestational age—New Ballard score.

## Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)							
Arm recoil							
Popliteal angle							
Scarf sign							
Heel to ear							

## Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	Maturity Rating
Plantar surface	Heel-toe 40-50 mm: -1 <40 mm: -2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	Score Weeks
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	-10 20
Eye/Ear	Lids fused loosely: -1 tightly: -2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	-5 22
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	0 24
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	5 26
							10 28
							15 30
							20 32
							25 34
							30 36
							35 38
							40 40
							45 42
							50 44

Neuro-muscular maturity	Physical maturity
Posture	Skin
Square window	Lanugo
Arm recoil	Plantar creases
Scarf sign	Breast
Popliteal angle	Eye/ear
Heel to ear	Genitalia (♂ & ♀)

# Pituitary Gland

(The master gland)

## Anterior Pituitary

- Somatotropes → GH (191 aa)
- Lactotropes → Prolactin (199 aa)
- Thyrotropes → TSH (Thyrotropin)
- Corticotropes → ACTH (Corticotropin)
- Gonadotropes → FSH, LH

These hormones are under the control of:

- Hypothalamic neurohormones: via the hypothalamo-hypophyseal portal circulation
- Feedback control

## Posterior Pituitary (Neural hormones)

- ADH (arginine vasopressin)
- Oxytocin

These hormones are synthesized in supraoptic & paraventricular nuclei of the hypothalamus and transmitted via the axoplasm to be stored in the posterior pituitary.

# Growth Hormone

- Pulsatile secretion more with sleep
- Action is mediated by insulin like growth factor-1 (*IGF-1*) or "somatomedin C" formed by the liver
- Action:
  1. Growth: ↑↑ Size of various tissues (bones, cartilage, muscles & viscera).
  2. Proteins: Anabolic.
  3. CHO: ↑↑ Gluconeogenesis.
  4. Lipids: ↑↑ Lipolysis.
  5. Electrolytes: ↑↑ Ca, ↑↑ Na, ↑↑ PO<sub>4</sub>
- Control of GH secretion:

Increase	Decrease
GHRH (GH-releasing hormone)	Somatostatin (also ↓↓ insulin, glucagon, gastrin, VIP)
Synthetic GHRH	Synthetic somatostatin analog ( <i>Octreotide</i> )
Hypoglycemia (Insulin)	Hyperglycemia
↑↑ aa (e.g., arginine)	
Clonidine, L-dopa, Glucagon	
Stress, Sleep, Exercise, Fasting	

# Hypopituitarism

## Definition

It is deficiency of GH with or without other pituitary hormones

## Etiology

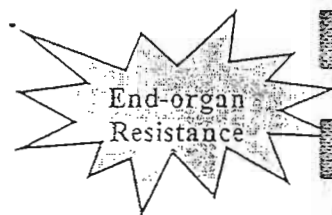
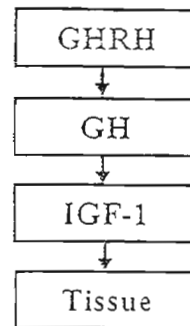
### I) Isolated GH deficiency:

#### A) Genetic

- GHRH receptor gene mutation
- GH gene mutation (AR, AD or X-linked)
- Biologically inactive GH
- GH receptor gene mutation (*Laron syndrome*): Autosomal recessive [↑↑ GH, ↓↓ IGF-1, No response to exogenous GH]
- IGF-1 gene mutation

#### B) Acquired

- Radiotherapy (leukemia)
- Idiopathic



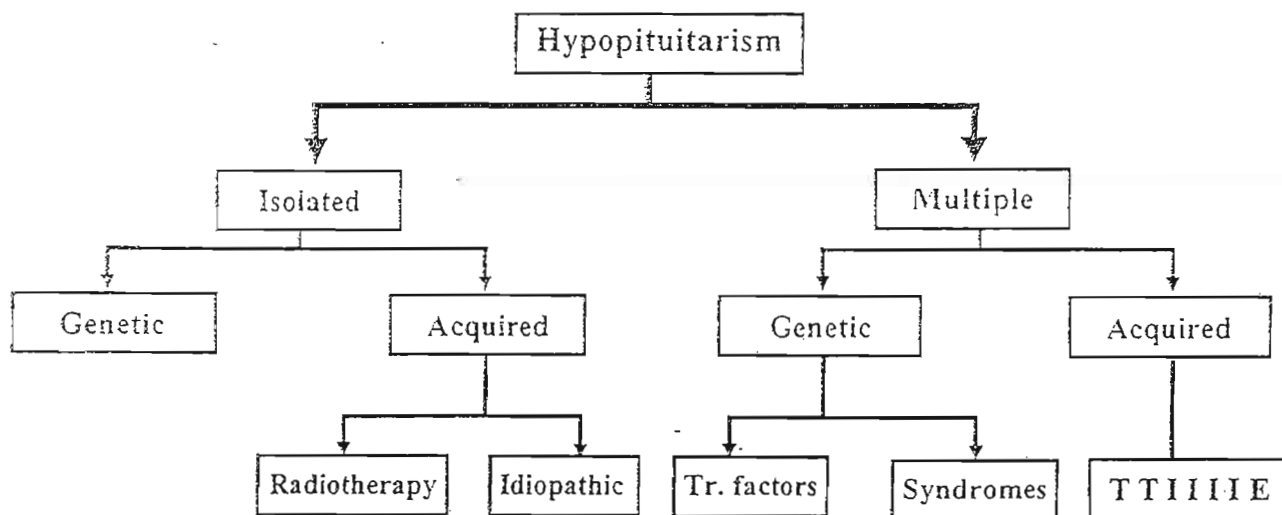
### II) Multiple pituitary hormone deficiency:

#### A) Genetic

- Mutations of transcription factors → Failure of transcription e.g. PROP1, LHX3, LHX4 gene mutation
- Congenital absence of the pituitary gland
- Anencephaly, encephalocele & hydrocephalus
- Septo-optic dysplasia (optic n. dysplasia & maldevelopment of septum pellucidum)
- Holoprosencephaly

#### B) Acquired

- Trauma: birth injury, child abuse, fracture base of skull, surgery
- Tumors: Craniopharyngioma, adenoma, germinoma, optic glioma
- Irradiation (GH deficiency precedes other hormones)
- Infection: meningitis & encephalitis
- Infiltration: histiocytosis X, hemochromatosis, sarcoidosis, TB, Toxoplasmosis
- Immune hypophysitis
- Empty-sella syndrome: congenital or following surgery or irradiation



## Clinical picture

### A) Congenital Hypopituitarism:

#### 1. At Birth:

- Normal weight & height
- Neonatal emergencies: apnea, cyanosis, hypoglycemia, seizures
- Prolonged neonatal jaundice (Conjugated)
- Microphallus in male is an important diagnostic clue

#### 2. Infancy & childhood:

- Profound proportionate postnatal growth failure (>2 SD below the mean for age & sex)
- Facies: rounded head, short face, prominent forehead, depressed nasal bridge, small nose, underdeveloped mandible, teeth (Delayed eruption & crowded)
- Intelligence: usually normal
- Sexual maturation: may be delayed
- Hypoglycemia (10%)

### B) Acquired Hypopituitarism:

#### 1. Hormonal manifestations:

- The child is normal initially
- Gradual onset & progressive course of growth failure
- Hypofunction of thyroid, adrenals and gonads
- Diabetes insipidus

#### 2. C/P of the cause:

- Pressure symptoms: ↑↑ ICT, optic atrophy, visual field defects, seizures
- Trauma, infection...

## Investigations

*Thyroid hormones are necessary for GH synthesis & action; so must be assessed before GH studies.*

### A) Laboratory:

#### 1. GH plasma level

GH level < 10 ng/ mL after 2 provocative tests is diagnostic

- Physiologic stimulation: Sleep (60 min), Exercise (20 min) ??
- Provocative agents: Insulin, clonidine, arginine, glucagon, L-dopa

Measuring GH level every 20 min over (12-24 hr) is used to diagnose *GH neurosecretory dysfunction*.

2. IGF-1: ↓↓ in all cases but ↑↑ with GH administration (except in Laron syndrome)
3. Other pituitary hormones: ACTH, TSH, ADH, Cortisol, T<sub>3</sub>, T<sub>4</sub> (Not FSH & LH)
4. Prolactin: Hyperprolactinemia strongly suggests hypothalamic lesion.
5. TRH stimulation test: ↑↑TSH & prolactin suggests hypothalamic lesion.
6. GHRH stimulation test: ↑↑GH suggests hypothalamic lesion.

### B) Imaging:

- Skull X-ray: beaten silver appearance, separation of sutures, enlargement of sella. destruction of clinoid processes & IC calcification (bone defects in histiocytosis)
- Long bones: delayed bone age.
- CT & MRI

**In hypothalamic lesions: ↓↓ all anterior pituitary hormones except prolactin**

## Treatment

1. Treatment of the cause: Surgery for tumors.
2. Replacement of pituitary hormones: Thyroid, hydrocortisone & late sex hormones.
3. Recombinant human GH (rHuGH)
  - *Dose*: 0.18-0.3 mg/kg/week, SC in 6-7 divided doses.
  - *Duration*: continuous till closure of epiphyses (NB: leoprolide may be used to delay puberty).

### *Criteria for stopping Rx:*

- Growth rate < 1 inch/year
- Bone age > 14 yr in ♀ & > 16 yr in ♂

### *- Side effects:*

- Leukemia.
- Hypothyroidism
- Pseudotumor cerebri
- Gynecomastia
- Slipped capital femoral epiphyses, worsening of scoliosis.
- Development of anti-GH antibodies (Rx with IGF-1)

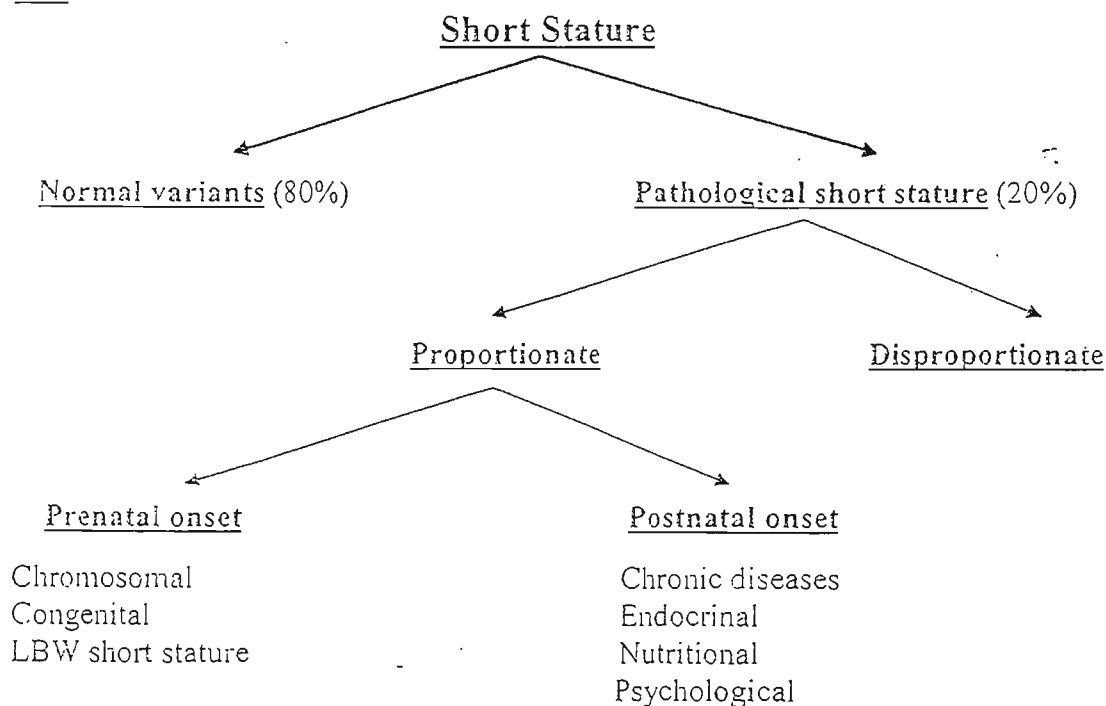
### *- Other indications of hGH:*

- |                    |  |
|--------------------|--|
| • Turner syndrome  | • IUGR   |
| • Noonan syndrome  | • Skeletal dysplasia                                 |
| • ESRD             | • Juvenile rheumatoid arthritis.                     |
| • Prader-Willi \$  | • Familial short stature (some patients may benefit) |
| • Silver-Russel \$ |  |

4. GHRH in hypothalamic causes.

5. Recombinant IGF-1: in Laron \$ & with the development of anti-GH antibodies

## DD Short stature.



# Short Stature

## Definition

Height more than 2 SD below the mean height for age & sex or < 5<sup>th</sup> percentile.

Pathologic short stature: Height >3 SD below the mean height for age & sex.

## Nomenclatures

Lower segment: Measured from the upper border of the symphysis pubis to the floor.

Upper segment: Total height – lower segment.

Arm span: Distance between the tips of middle fingers when the arms are fully extended.

Supine length: (birth to 2-3 yrs). The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard. The head should be in the "Frankfurt plane" (ear hole to lower border of eye socket).

Standing height: measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane".

## U/L ratio:

- At birth: 1.7 (Umbilicus is in the middle)
- At 3 yrs: 1.3
- At 7 yrs: 1 (Symphysis is in the middle)

## Arm span – height:

- 1<sup>st</sup> 7 yrs: -3
- 8 -12 yrs: Zero

## Classification

### A) Proportionate or Disproportionate

1. Proportionate short stature: normal values are obtained
2. Disproportionate short stature: abnormal values are obtained

### B) Type of short stature

1. Short limbs
2. Short trunk

Ratio	Short Limbs	Short Trunk
U/L	High	Low
Arm span/Height	Low	High

### C) Classification of short limbs

1. Rizomelic: proximal shortening of humerus & femur (e.g., achondroplasia)
2. Mesomelic: middle segment shortening of radius & ulna, tibia & fibula.
3. Acromelic: terminal shortening of fingers.

## MPH & TCR

Mean parental height = (Father's height + Mother's height) / 2

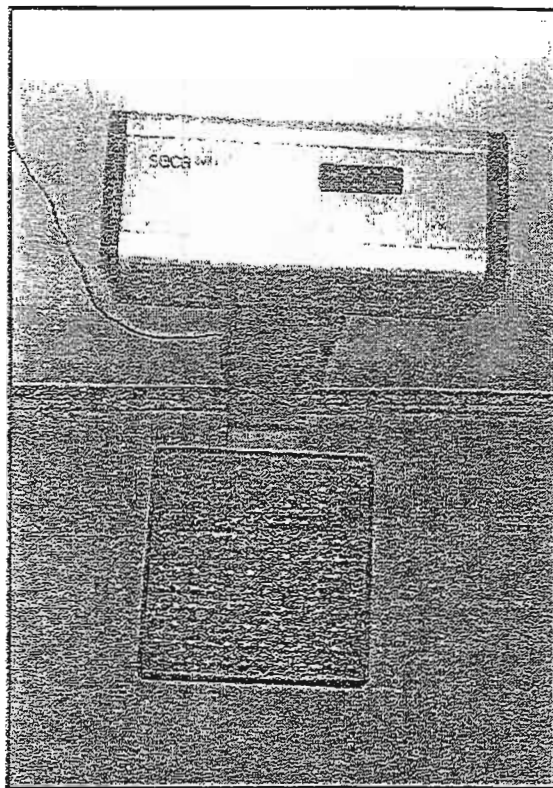
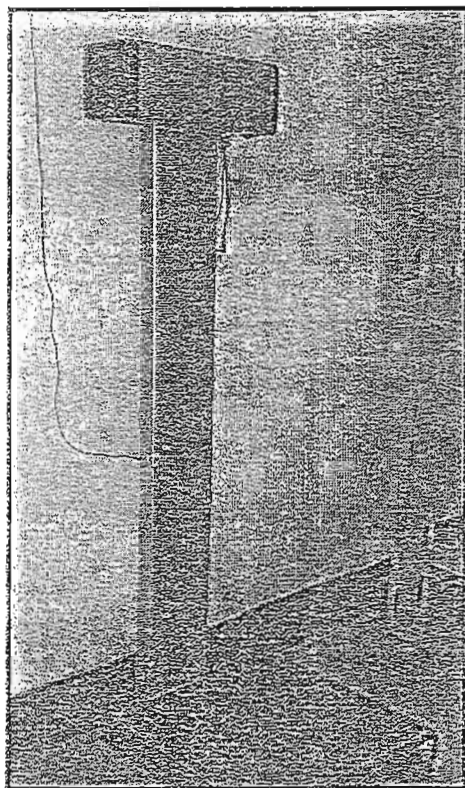
Mid Parental Height (MPH) for ♂ = Mean parental height + 7

Mid Parental Height (MPH) for ♀ = Mean parental height - 7

Target Centile Range (TCR) for ♂ = MPH ± 12

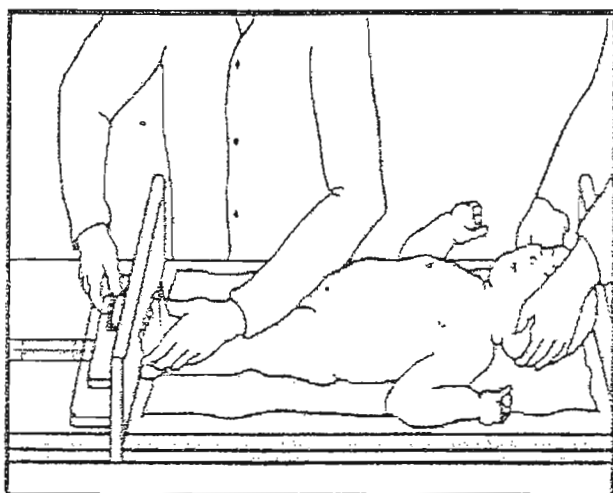
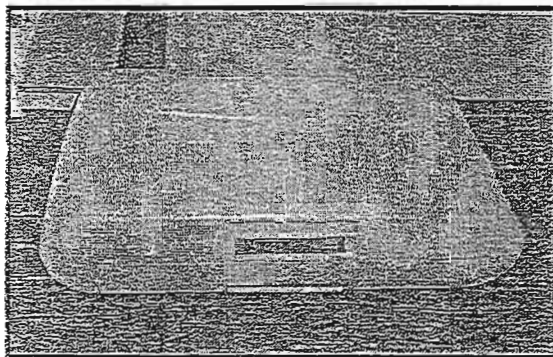
Target Centile Range (TCR) for ♀ = MPH ± 11

# Instruments for Weight & Height Measurement

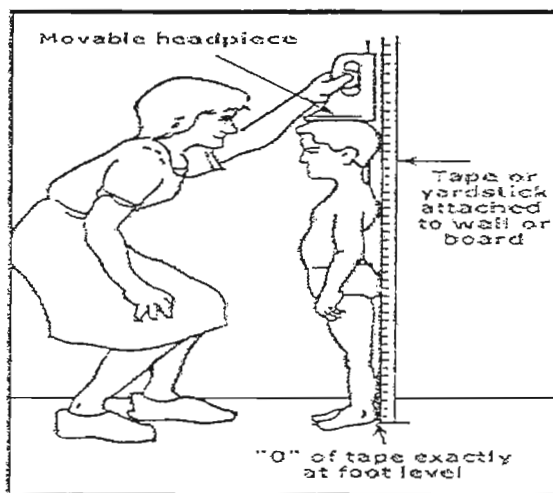


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer  
Height is measured using stadiometer



## Etiology

### A) Normal variants (80%)

	1. Familial (genetic)	2. Constitutional growth delay
Family history	Positive (parents are short)	Positive
Growth velocity	Normal	Period of transient decelerated growth
Bone age	Normal	Delayed
Puberty	Normal	Delayed
Adult height	Short adult height	Normal adult height
Treatment	GH may be useful	Reassurance

### B) Pathological (20%)

#### 1. Endocrinal

- Hypothalamus: Laronce-Moon Biedl
- Pituitary: Hypopituitarism
- Thyroid: Congenital hypothyroidism
- Suprarenal: Cushing, CAH
- Gonads: Precocious puberty
- Pancreas: DM

#### 2. Chronic debilitating diseases

- CVS: CHD, RHD
- Resp.: TB, Cystic fibrosis, asthma
- Renal: CRF, RTA, DI
- GIT: Malabsorption, IBD
- Immunodeficiency
- Hepatic: Cirrhosis, Wilson's
- Collagen: JRA
- Blood: Chronic hemolytic anemia
- Infection: TB, suppurative lung S.
- Metabolic: aa, organic acidemias

#### 3. Chromosomal

- Turner
- Down
- Trisomy 18

#### 4. Congenital syndromes

- Prader-Willi
- Silver-Russel
- Cornelia De Lange (microcephaly, synophrys...)
- Progeria

#### 5. Metabolic

- Aminoacidopathies
- Organic acidemias
- Storage diseases (Gaucher, NP...)
- Minerals: Cu, Fe...

#### 6. Psychological (deprivation) dwarfism

- Disturbed child-mother or family relation → ↓↓ GH release (Unknown mechanism)
- Growth will be resumed if the child is provided with love & care (i.e., Catch-up)
- Bone age is delayed

#### 7. Malnutrition: Malnutrition → ↓↓ Synthesis of GH mediators (Growth factors)

#### 8. Skeletal (=Causes of Disproportionate short stature)

- Rickets
- Achondroplasia (large head, short limbs & normal trunk) + Normal mentality
- Hypochondroplasia (normal head - Features are not prominent as achondroplasia)
- Osteogenesis imperfecta (osteoporosis + multiple fractures + blue sclera + hearing ↓)
- Mucopolysaccharidoses
- Chondroectodermal dysplasia (short limbs + ectodermal dysplasia + polydactyly + CHD)

#### 9. Primordial short stature (LBW short stature)

- IUGR (Congenital infections, Congenital malformation, placental insufficiency)
- Silver-Russel syndrome (triangular face, incurved 5th finger, hemihypertrophy)
- Seckel syndrome (Bird-headed dwarfism)

#### 10. Drugs: Steroids

## Approach to a case of short stature

### (A) History:

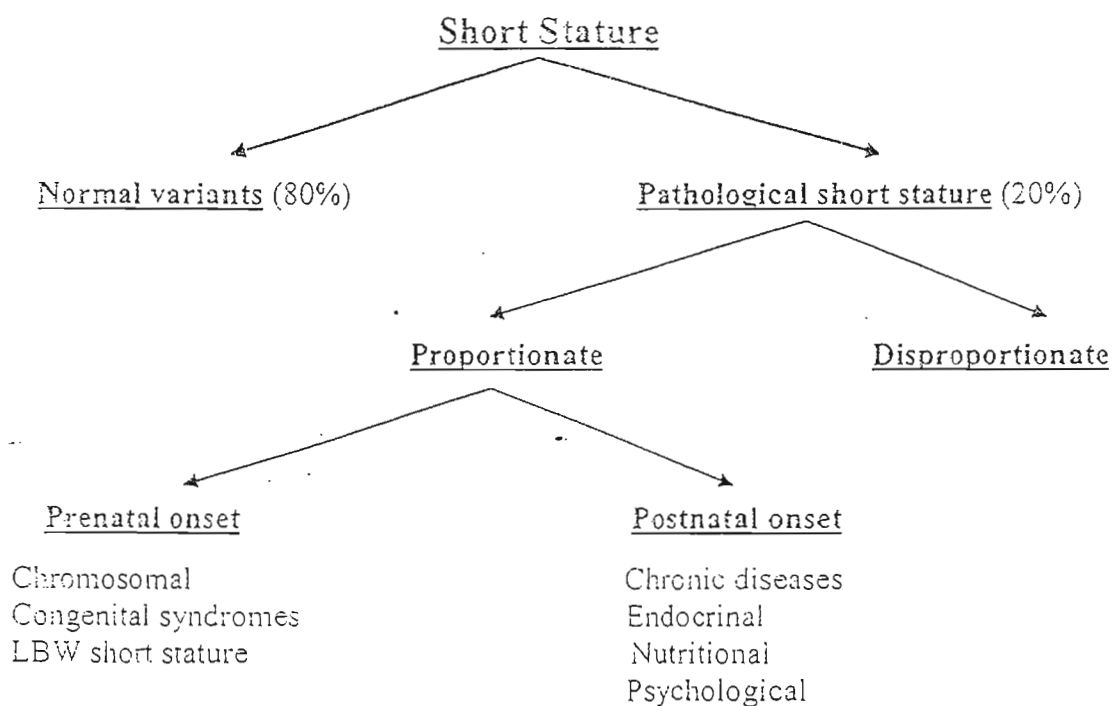
- Symptoms of different system affection
- Nutritional history
- Perinatal history: Birth length & weight, causes of IUGR
- Psychological assessment
- Parental heights & TCR

### (B) Physical examination:

- Measure height/length, US & LS, arm span → Proportionate or disproportionate
- Manifestations of chromosomal abnormalities (e.g., Turner...), congenital syndromes (e.g., Prader-Willi), hypopituitarism (microphallus)
- Complete system examination.

### (C) Investigations:

- CBC, ESR, UA, electrolytes, KFTs, LFTs
- Karyotyping is routine in all ♀ with short stature
- Bone age (Lt wrist X-ray): normal in familial cases & skeletal dysplasia
- Imaging: CT, MRI
- Investigations of endocrinal causes (start with thyroid): *See before*



# Tall Stature

## Definition

Height more than 2 SD above the mean height for age & sex or > 97<sup>th</sup> percentile.

## Etiology

1. Familial (genetic or constitutional)
    - +Ve family history.
    - Normal bone age
    - Normal puberty
    - Tall adult height.
  2. Exogenous obesity
  3. Precocious puberty
  4. Hyperthyroidism
- } →
- Advanced bone age
  - Tall child height
  - Normal adult height
5. Marfan: ↑↑ arm span, ↓↓ US/LS
  6. Homocystinuria:
  7. Klinefelter (XXY) & XYY syndrome
  8. McCune-Albright syndrome
  9. Cerebral gigantism (Sotos syndrome):
    - Growth rate: -At birth → Macrosomic      -1-5 yrs: accelerated rate of growth
    - >5 yrs → Normal growth rate      - Normal adult height
    - Physical: Large head, dolicocephaly, hypertelorism, prominent jaw, large hands & feet
    - Mental: MR
    - Sexual: Normal
    - ↑↑ Risk of malignancy (Wilms, liver)
    - Normal endocrinal studies.
  10. GH excess
    - Open epiphyses → Gigantism
    - Closed epiphyses → Acromegaly

(Skull, coarse facies hands, feet, jaw, tongue, kyphosis, IGT)

## Etiology:

- ☒ Hyperplasia
- ☒ Adenoma (GH-secreting)

## Investigations:

- ↑↑ GH (No ↓↓ with hyperglycemia)
- ↑↑ IGF-1
- ↑↑ Prolactin (in case of pituitary adenoma secreting both GH & prolactin)
- ↓↓ Pituitary hormones (compression by adenoma)
- Skull X-ray, CT & MRI brain

## Treatment:

- Surgical removal of adenoma
- Irradiation (hypopituitarism)
- Somatostatin analogues (*Octreotide*)
- Bromocriptine (dopamine agonist) in cases with ↑↑ prolactin
- GH receptors antagonist (*Pegvisomant*)

Dopamine = Prolactin-inhibiting factor

### Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann S
3. Cerebral gigantism (Sotos)
4. IGF-II excess

### Treatment of familial tall stature

♂ → Testosterone enanthate

♀ → Ethinyl estradiol

**When:** Predicted adult height > 3 SD.

Severe psychological impairment

# Puberty

## Definition

It is the period of life during which the endocrine & gametogenic functions of the gonads have developed to the point where reproduction is possible [physical & sexual maturation]

## Adolescence

It is the period of life during which child becomes an adult [Physical, sexual, psychological & social maturation]. So, puberty is 1<sup>st</sup> part of adolescence.

## Physiology of Puberty

Sex hormones = Testosterone & Estrogen

- Prepubertal stage:
  - Hypothalamo-hypophyseal-gonadal axis is dormant (upper neuronal inhibition)
  - ↑↑ Sensitivity of H-H-G axis to sex hormones
  - LH & sex hormones: undetectable
- 1-3 yrs before puberty:
  - GnRH & LH pulsatile secretion start to occur first, during sleep
  - Gradual ↑↑ in amplitude & frequency of GnRH & LH pulses
  - Adrenarche: ↑↑ adrenal androgens (responsible for pubic hair, acne, voice...)
- During puberty:
  - GnRH & LH pulsatile secretion occur at 90-120 min intervals
  - No more diurnal variation
  - In ♀, +Ve feedback effect of estrogen causing LH surge in midcycle (ovulation)

## Age of Onset of Puberty (Variable)

♀ = 8-13 yrs      ♂ = 9-14 yrs

## Factors affecting the age of Onset of Puberty

1. Osseous maturation (bone age):
  - The onset of puberty is more closely related to osseous maturation than to chronological age
  - Estrogen is responsible for bone maturation & epiphyseal closure in both ♀ & ♂
2. Genetic factors
3. Nutrition: Good nutrition → earlier puberty
4. Body build: Moderate obesity → earlier puberty, Morbid obesity → delayed puberty
5. Physical activity (energy balance): ♀ athletes (ballet dancers & swimmers) → delayed puberty

## Physical changes of Puberty

### ☒ Females:

- First sign of puberty is breast enlargement
- Followed by → Pubic hair → Axillary hair → Menarche
- Average age of menarche in Egyptian ♀ is 12.5 yrs
- Less obvious changes: ↑↑ Ovaries, uterus, labia & thickening of vaginal mucosa

### ☒ Males:

- First sign of puberty is testicular enlargement (Prader orchidometer)
- Followed by → Thinning & pigmentation of the scrotum → ↑↑ Penis → Pubic hair → Axillary hair
- Less obvious changes: ↑↑ epididymis, seminal vesicles, prostate & gynecomastia (65%)

- Prader orchidometer (12-ellipsoids): 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25 ml
- Testicular volume: Preadolescence = 1-3 ml
- Testicular length (exclude epididymis): Preadolescence = 1.5-3 cm

## Stages of Puberty (= Tanner staging)

### ☒ Females:

Stage	1. Pubic Hair	2. Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

### 3. Axillary hair (3 stages)

- No
- Appearance
- Adult type

### ☒ Males:

Stage	1. Pubic Hair	2. Penis	3. Testes
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, at the base of the penis	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth )	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

### 4. Axillary hair (as in females)

## Secondary Sex Characters

2ry Sex Ch.	Male	Female
Voice	Deep	High pitched
Hair distribution	Beard, frontal baldness. chest, pubic hair (triangle with apex up)	Less body hair, ↑↑ scalp hair, pubic hair (triangle with base up)
Body shape	Masculine	Fat distribution (breast & buttocks)
skeleton	Wide shoulders, Narrow hips	Narrow shoulders, wide hips
Libido	↑↑ Libido	↑↑ Libido

## Growth

- Definition: Increase in the size & number of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Fetal: Fastest period of growth (*See factors affecting IU growth*)
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone (& Thyroxine)
  - Puberty: Sex hormones (& Growth hormone)

## Pubertal growth spurt

It is divided into 3 phases:

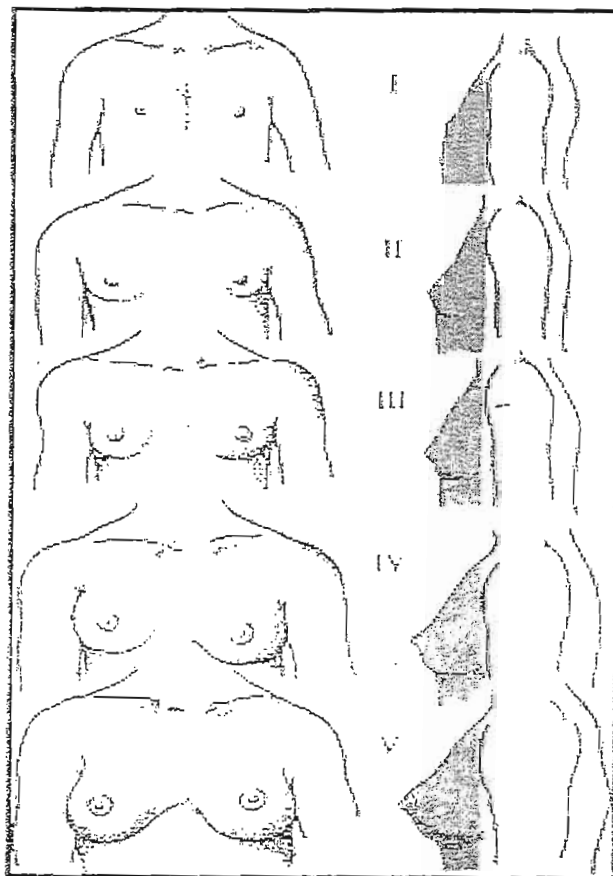
- Take-off = Minimum growth velocity
- Peak height velocity = Maximum growth velocity
- Decelerated phase

### ☒ Females:

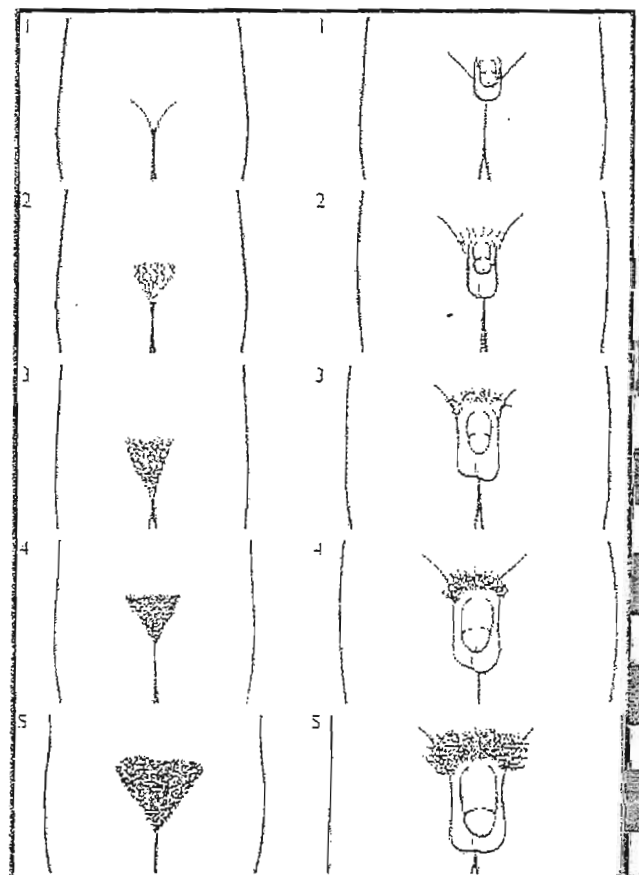
- Onset of peak height velocity = pubertal stage 2-3 [i.e., pre-menarcheal event]
- Height gain = 25 cm

### ☒ Males:

- Onset of peak height velocity = pubertal stage 3-4 [2 yrs after females]
- Height gain = 28 cm [Mean height difference between ♂ & ♀ = 13 cm, why??]



Tanner staging of female breast changes



Tanner staging of pubic hair

# Cushing Syndrome

## Definition

Increased level of cortisol with hypertension and characteristic pattern of obesity

## Etiology

### A) Exogenous Cushing Syndrome (Cushinoid Syndrome)\*:

Prolonged therapy with:

- ACTH
- Steroid

### B) Endogenous Cushing Syndrome:

#### ☒ ACTH dependent:

- a. Cushing disease: ACTH secreting pituitary adenoma (microadenoma)  
→ Bilateral adrenal hyperplasia (most common in children > 7 yrs)
- b. Ectopic ACTH: Pancreatic islet cell carcinoma, neuroblastoma, Wilms tumor

#### ☒ ACTH-independent (adrenal):

- a. Functioning adrenocortical tumor: in infancy (Malignant\* or benign)
- b. Primary pigmented nodular adrenocortical disease: multiple, small pigmented nodules
- c. McCune-Albright syndrome (autonomous hyperfunction)
- d. Multiple Endocrine Neoplasia (MEN) type I

## Clinical picture

- Characteristic obesity: Moon face, flushed plethoric face, doubled chin, trunkal, buffalo hump, thin limbs, striae rubra (abdomen & thigh).
- Delayed healing of wounds
- Osteoporosis → pathologic fractures and kyphosis
- Muscle weakness & myopathy
- Hyperglycemia
- Short stature
- Increased susceptibility to infection
- Hypertension → Heart failure
- Hypokalemia → Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany
- Androgen excess → Hirsutism, acne, deep voice, accelerated growth & clitoromegaly
- Adolescent female → Amenorrhea & hirsutism

## Investigations

### A) Diagnosis of Cushing Syndrome:

Laboratory:

- ↑↑ Na, ↓↓ K, ↓↓ H<sup>+</sup> (metabolic alkalosis)
- ↑↑ Glucose, OGTT
- CBC → ↑↑ RBC, ↑↑ PNLs, ↓↓ Lymphocytes, ↓↓ eosinophils

Hormonal:

- Cortisol level: loss of circadian rhythm then persistent elevation
- ↑↑ Salivary cortisol level (screening)
- ↑↑ Urinary cortisol & 17(OH) corticosteroids
- Single dose dexamethasone suppression test (25 µg/Kg) → No ↓↓ in Cortisol level

3

## B) Diagnosis of the etiology of Cushing syndrome:

### Hormonal:

- Plasma ACTH
  - a. ACTH dependent → ↑↑ ACTH
  - b. Non-ACTH dependent → ↓↓ ACTH
- CRH stimulation test:
  - a. ACTH dependent → ↑↑ ACTH & cortisol
  - b. Non-ACTH dependent → No response (Pituitary is suppressed)
- Dexamethasone suppression test [ $D_1$  30 µg/Kg/day qid,  $D_2$  120 µg/Kg/day qid]
  - a. ACTH dependent → ↓↓ Cortisol
  - b. Non-ACTH dependent → No response

### Imaging:

- X-ray: Osteoporosis, advanced bone age, ↓↓ thymic shadow
- Brain CT, MRI: Pituitary microadenoma
- Abdominal US, CT, MRI: adrenal adenoma

## Treatment

1. Adrenal tumors: surgical removal
  - a. Benign → Subtotal adrenalectomy
  - b. Malignant → Total adrenalectomy
 + Replacement therapy (Cortisol & ACTH)
2. Pituitary adenoma (Cushing disease):
  - a. Pituitary irradiation (?? Hypopituitarism)
  - b. Surgical removal (Transphenoidal approach)
  - c. Total adrenalectomy: may be followed by the development of locally invasive pituitary tumor → ↑↑ ACTH → Hyperpigmentation (= *Nelson syndrome*)
  - d. Cyproheptadine (Centrally acting serotonin antagonist → # ACTH release)

# Obesity & Overweight

## Definition

- Obesity: BMI > 95<sup>th</sup>% for age & sex. (In adults BMI > 30 Kg/m<sup>2</sup>)
- Overweight: BMI = 85-95<sup>th</sup>% for age & sex
- Body mass index (BMI) = Weight (Kg) / Height<sup>2</sup> (meters)
- BMI also ↑↑ in body builders due to ↑↑ muscle bulk
- More than 22 millions children < 5 years are overweight

## Classification

### A) Exogenous obesity: [Most common]

#### Etiology: Multifactorial

- a. Gene-environment interaction
- b. Genetic control of energy expenditure (specific set point for body weight)
  - ↓↓ Energy expenditure → ↑↑ Risk of obesity
- c. Environmental
  - Type of food: ↑↑ calories, ↑↑ CHO, ↑↑ Fat, highly processed
  - Physical activity: TV watching, games, computers
- d. Heredity (parental obesity specially maternal, familial)
- e. Leptin deficiency or resistance: (↑↑ food intake & ↓↓ energy expenditure)



Clinical picture:

- Tall stature (Adult height is normal or low)
- Advanced bone age & early puberty
- Acanthosis nigricans (hyperpigmented hyperkeratotic skin lesion usually in the post. neck or axilla). It is a clinical marker of insulin resistance & ↑↑ risk of type 2 DM

Prevention:

1. Change dietary habits & ↑↑ physical activity
2. Breast feeding → ↓↓ risk of obesity

Treatment:

1. Dietetic: ↓↓ CHO, ↓↓ fat, ↓↓ calories, ↑↑ fibers
2. Life style: ↓↓ TV watching, ↑↑ physical activity
3. Drugs "Not very promising"
  - ↓↓ Food intake → Sympathomimetics, MAO inhibitors
  - ↑↑ Energy expenditure → Ephedrine, caffeine
  - ↓↓ Fat absorption → Orlistat
4. Recombinant leptin: ↓↓ weight, ↑↑ energy expenditure
5. Surgical gastroplasty

**B) Endocrinal:**

- Hypothalamic lesions: Encephalitis, tumors (craniopharyngioma, optic glioma)
- Frolich syndrome: Dwarfism, polyphagia, obesity, DI, hypersomnia
- Cushing syndrome
- Hypothyroidism
- Pseudohypoparathyroidism
- Stein-Leventhal S: Obesity, hirsutism, amenorrhea, infertility, polycystic ovaries, inverted FSH / LH ratio (Normally FSH > LH)

**C) Congenital syndromes:**

- Laurant-Moon-Biedle S: Obesity, short stature, mental retardation, polydactyly, syndactyly, retinitis pigmentosa, hypogonadism
- Beckwith-Wiedemann S: Fetal overgrowth, macrosomia, macroglossia, polycythemia, visceromegaly (HSM& nephromegaly), omphalocele, hemihypertrophy, hypoglycemia, characteristic ear lobe crease, ↑↑ risk of neoplasms (Wilms tumor)
- Prader-Willi S: Hypotonia, hypogonadism, mental retardation, short stature, small hands& feet, early FTT followed by rapid weight gain (1-6 yrs), polyphagia & obesity

Genetics of Prader-Willi:

- Deletion of paternally acquired segment of chromosome 15
- Maternal disomy (Both chromosomes 15 are from the mother)
- (NB: Paternal disomy of chromosome 15 → Angelman syndrome)

**C) Chromosomal:**

- Turner (XO)
- Klinefelter syndrome (XXY)
- Down (Trisomy 21)
- XXXXY syndrome

Complications of obesity

1. CVS → HTN, ischemic heart disease, hyperlipidemia& atherosclerosis
2. Respiratory → Sleep apnea, Pickwickian S, restrictive hypoventilation
3. CNS → Pseudotumor cerebri, social& behavioral problems
4. GIT → Fatty liver, cholesterol gall stones, GERD
5. Endocrine → Insulin resistance, type 2 DM, early puberty, Stein-Leventhal S
6. Joints → Slipped femoral epiphyses
7. Social & behavioral problems

Approach to a case of obesity:

Dietetic history, Stature, BP, Mentality, Syndromic

# Hypogonadism

## Definition

- Delayed sexual development with no evidence of puberty by the age 13 in ♀ & 14 in ♂
- Causes include: Constitutional, hypogonadotropic & hypergonadotropic hypogonadism

Male Hypogonadism	Female Hypogonadism
<b>(A) Primary hypogonadism</b> (= Hypergonadotropic-hypogonadism) Testicular defect ↑↑ Gonadotropins	<b>(A) Primary hypogonadism</b> (= Hypergonadotropic-hypogonadism) Ovarian defect ↑↑ Gonadotropins
<b>(B) Secondary hypogonadism</b> (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)	<b>(B) Secondary hypogonadism</b> (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)

## Male Hypergonadotropic-Hypogonadism

### Etiology

1. Congenital anorchia: Testicular damage after sexual differentiation
2. Defects of androgen production: see before (46 XY-DSD)
3. Rudimentary testes: (AR or XLR) "Very small testes"
4. Germ cell aplasia (Del Castillo \$ or Sertoli cell only\$):
  - Leydig cells: normal → normal testosterone → normal sexual differentiation
  - Seminiferous tubules (absent Sertoli cells) → Small testes, azoospermia, infertility
  - No inhibin (normally secreted by Sertoli cell) → ↑↑ FSH with normal LH
5. Klinefelter (47, XXY male): (1/1000)
6. 45, X male: Yp segment is translocated to another chromosome
7. XX male: Paternal X-Y Crossing over involving SRY gene
8. XXX male: Paternal X-Y Crossing over AND maternal X-X non-disjunction
9. Noonan Syndrome: (1/1000)
10. Testicular damage
  - . Bilateral torsion (Vascular)
  - . Surgical trauma during correction of cryptorchidism
  - . Radiotherapy & chemotherapy
  - . Acute orchitis: Mumps in pubertal ♂

### Noonan Syndrome:

- o Etiology: AD (variable expression)
- o Features of Turner \$ + Normal karyotyping + affecting ♀ & ♂
- o Short stature, neck webbing, cubitus valgus
- o CHD: PS
- o Facies: Hypertelorism, epicanthus, ptosis, micrognathia, antimongloid slant, ear anomalies
- o Hypogonadism: Delayed puberty (2 yrs later)
  - ♂: Small testes, cryptorchidism
  - ♀: Premature ovarian failure
- o Mental retardation: 25%
- o Rx: hGH

### Klinefelter Syndrome:

#### Genetic types:

- . Non-disjunction (most common)
- . Mosaicism (better prognosis)
- . Variants: XXXY, XXXXY (↑↑ Severity)

C/P: as in ♂ 1ry hypogonadism + some MR + learning disability + behavioral disorders

#### Investigations:

#### Complications:

Breast cancer, mediastinal germ cell tumors  
Rx:

### Poly-Y male (47, XYY male):

No Hypogonadism

Aggressive antisocial behavior & violence

## Clinical picture

1. Onset: Usually present as delayed puberty  
May be suspected at birth (Micropenis & small testes)
2. Measurements: Tall stature; span > height, LS > US (*Eunuchism*)
3. Testes: Absent or small (Prader Orchidometer)
4. Secondary sex characters fail to develop:
  - o Hair (facial, axillary, pubic): scanty
  - o Acne: absent
  - o Voice: high pitched
  - o Fat distribution: feminine (buttocks, breast)
  - o Penis & scrotum: infantile
5. Gynecomastia
6. Infertility (Azoospermia)
7. Picture of the cause



## Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. hCG stimulation test: No response [Normally hCG → ↑↑ Testosterone at any age]
4. AMH & Inhibin level
5. Karyotyping (XXY...)
6. Azoospermia
7. Testicular biopsy (In Klinefelter \$: Hyalinized seminiferous tubules)

### Side Effects of sex steroids

- Lipid abnormalities
- Thromboembolism
- Acne
- HTN

## Treatment

- Long-acting testosterone enanthate, starting at 11-12 yrs (Why?)  
Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks
- Intracytoplasmic sperm injection (ICSI): ?? fertility

# Male Hypogonadotropic-Hypogonadism

## Etiology

1. Hypopituitarism: Transcription factors & TTHIIIIE
2. Isolated deficiency of gonadotropins:
  - Sporadic
  - Familial
3. Genetic defects:
  - Kallmann \$ (XLR, AR, AD) "hypogonadism, anosmia, mid-facial & renal defects"
  - DAX-1 gene mutation causing adrenal hypoplasia & impaired GnRH secretion
4. Congenital syndromes
  - Laurant-Moon Biedl
  - Prader-Willi

## Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (Microphallus in hypopituitarism, anosmia in Kallmann \$)

## Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↓↓ with absence of nocturnal pulsatile LH secretion
3. hCG stimulation test: ↑↑ Testosterone
4. GnRH stimulation test: Blunt GTH response (DD: Constitutional delayed puberty)
5. Other pituitary hormones (GH, ACTH) & imaging
6. DNA probes for different mutations (Kallmann \$)

## Differential Diagnosis

• Constitutional delayed puberty: "Not uncommon = 3 %"

Diagnosis: If no puberty (Testicular volume < 4 mL) by the age of 14-15 yrs & testosterone level < 50 ng/dL. It should be differentiated from hypogonadotropic-hypogonadism;

- Family history: +Ve
  - Single 8 A.M. Testosterone level: is a good predictor of impending puberty
  - Nocturnal pulsatile LH secretion: may be detected
  - GnRH stimulation test: ↑↑ LH
  - Treatment: Testosterone enanthate, 100 mg IM/4 wks, for 4-6 months
- Value:
- Increase 2ry sex characters (relieves anxiety)
  - May initiate puberty (↑↑ Growth & ↑↑ Bone age)
  - DD: from Hypogonadotropic-hypogonadism (Diagnostic therapeutic test)

## Treatment

- Constitutional delayed puberty should be ruled out
  - Established cases (pubertal changes regress after discontinuation of testosterone):
- a. Testosterone enanthate, starting at 11-12 yrs  
Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks →  
Development of 2ry sex characters but with *small sized testes*
  - b. hCG (*Pregnyl*): IM 500-1000 IU, 3 times weekly → stimulates testicular growth & spermatogenesis. If testicular ↑↑ is not sufficient after 6-12 months, add:
  - c. Human menopausal gonadotropin (HMG) "*Humegon*": IM 37.5-150 IU, 3 times/ wk
  - d. Episodic administration of GnRH: programmable infusion pump (Very expensive)

## Prognosis

Spermatogenesis can be achieved after proper Rx (up to 2 yrs)

# Female Hypergonadotropic-Hypogonadism

## Etiology

1. Turner syndrome (45, XO): (1/2000)
2. Noonan S: Differences??
3. XX Gonadal dysgenesis (Pure gonadal dysgenesis): Gonads as Turner, No somatic features
4. Mixed gonadal dysgenesis: see before
5. XXX female: Non disjunction, No hypogonadism, learning & behavioral disorders
6. XXXX & XXXXX female: Hypogonadism + MR
7. Resistant ovary syndrome: FSH receptor defect
8. Ovarian damage
  - Radiotherapy & chemotherapy
  - Galactosemia
  - Denys-Drash syndrome
  - Ataxia telangiectasia
  - Immune ovarian failure

	Turner	Noonan
Sex	Only ♀	♀ & ♂
Genetics	Non-disjunction	AD
Cardiac	CoA / bicuspid aortic valve	PS
Mentality	MR in 18%	MR more common
Sexual Development	Hypogonadism	Delayed (2yrs)

# Turner Syndrome

## Genetic Types

- ☑ Non-disjunction (most common): The X chromosome is usually of maternal origin
- ☑ Mosaicism (better prognosis): 45, X / 46, XX

## Clinical picture

(A) At birth: Edema of dorsum of hands & feet

(B) Childhood:

- |                                      |   |
|--------------------------------------|---|
| - Short stature (mean = 143 cm)      | - Normal mentality (MR in 18%)                |
| - Webbing of the neck                | - Cardiac: Coarctation, bicuspid aortic valve |
| - Widely spaced nipples              | - Renal: Horseshoe, ectopic kidney...         |
| - Cubitus valgus (↑↑ carrying angle) | - Thyroiditis (30%)                           |
| - Low posterior hair line            | - IGT, Type II DM                             |

(C) Puberty:

- Secondary sex characters fail to develop

## Investigations

1. Estrogen level: ↓↓
2. Gonadotropins "FSH& LH": ↑↑ (specially > 11 yrs)
3. Karyotyping (45, X)
4. U/S, Echocardiography, Thyroid profile

## Treatment

- hGH
- Estrogens: To induce the development of 2ry sex characters. Start at 11-12 yrs (Why?)
- Estrogen + Progesterone cyclic therapy:
  - Estrogen D1- D23
  - Progesterone D10- D23
  - No Rx D23-D30 → Withdrawal bleeding
- Ovum donation + IVF: ?? Fertility

# Female Hypogonadotropic-Hypogonadism

## Etiology

1. Hypopituitarism: Transcription factors & TTHHE
2. Isolated deficiency of gonadotropins:
  - Sporadic
  - Familial
3. Genetic defects:
  - Kallmann S (XLR, AR, AD) "hypogonadism, anosmia, mid-facial & renal defects"
4. Congenital syndromes
  - Laurence-Moon Biedl
  - Prader-Willi
5. Anorexia nervosa

## Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (anosmia in Kallmann syndrome)

## Investigations (as in 2ry ♂ hypogonadism)

## Treatment Constitutional delayed puberty should be ruled out

# Gynecomastia

## Definition

Enlargement of the male breast due to hypertrophy of the glandular tissue

## Etiology

1. Physiological
  - a. Neonatal: Transplacental passage of maternal estrogens
  - b. Pubertal (65% of all ♂): ↑↑ aromatase activity. Bilateral or unilateral & tender
2. Pathological
  - a. Endocrinal: Male hypogonadism (Klinefelter syndrome)
  - b. Liver cell failure (↓↓ estrogen metabolism)
  - c. Neoplastic: Feminizing tumors (testicular & adrenal)
    - Prolactinoma
    - Bronchogenic carcinoma (Paramalignant syndrome)
  - d. Drugs: Estrogens, spironolactone, digitalis, cimetidine, ketoconazole
  - e. Idiopathic

# Cryptorchidism

## Definition

Failure of descent of one or two testes

DD of empty scrotum:

1. Absent testes
2. Retractable testes
3. Undescended testes

## Incidence

Term = 3.4%      Preterm = 30%      Spontaneous descent occurs in the majority  
 If No descent by the age of 4 months, the testis will remain undescended

## Factors affecting testicular descent

1. Hormonal
  - Testosterone, DHT & AMH
2. Mechanical
  - Gubernaculum, epididymis & abdominal pressure

Retractable testis:

Brisk cremastic reflex  
 Testes can be brought down to the scrotum

## Classification

1. Abdominal
2. Inguinal
3. Gliding
4. Ectopic (Superficial inguinal, perineal)

## Investigation

1. Testosterone before & after hCG stimulation: to detect functioning testicular tissue & exclude anorchia
2. U/S, CT, MRI abdomen
3. Laparoscopy

## Complications

1. Infertility (Testicular pathological changes start to occur by 6-12 months)
2. Malignancy (1/40-80)
3. Psychological

## Treatment (Before 9-15 months, ideally at 6 months)

1. Hormonal
  - a. hCG (Pregnyl): IM 3000 IU/ wk for 4 weeks; or
  - b. GnRH
2. Surgical (Orchidopexy)

Cairo University, Faculty of Medicine

Time Allowed 1.5 hrs

Pediatric Department

Total Marks 25

M.Sc. Pediatrics

Second part

### Genetics

Answer the following questions:

- 1- Enumerate 5 characters of X-linked dominant mode of inheritance. (5 marks)
- 2- Enumerate 5 clinical features that are suggestive of Turner syndrome (5 marks)
- 3- Non invasive investigations for prenatal diagnosis of Down syndrome. (5 marks)

Problem solving (5 marks)

Five year old child with pectus excavatum, dislocated lenses of the eyes and a heart murmur his uncle developed aortic dilatation and insufficiency at age 41.

What is the most likely diagnosis?

What is the mode of inheritance?

What is the diagnostic confirmatory test?

Multiple choice questions :

1- A baby born with pulmonary hypoplasia secondary to oligohydramnios caused by renal agenesis would be classified as having

- a- An association
- b- A dysplasia
- c- A sequence
- d- A syndrome

2- The pattern of inheritance shown by malignant hyperthermia is

- a- autosomal dominant
- b- autosomal recessive
- c- X-linked dominant
- d- X-linked recessive

3- The DiGeorge/Shprintzen syndrome is caused by deletion in which chromosome

- a. 4
- b. 7
- c. 15
- d. 22

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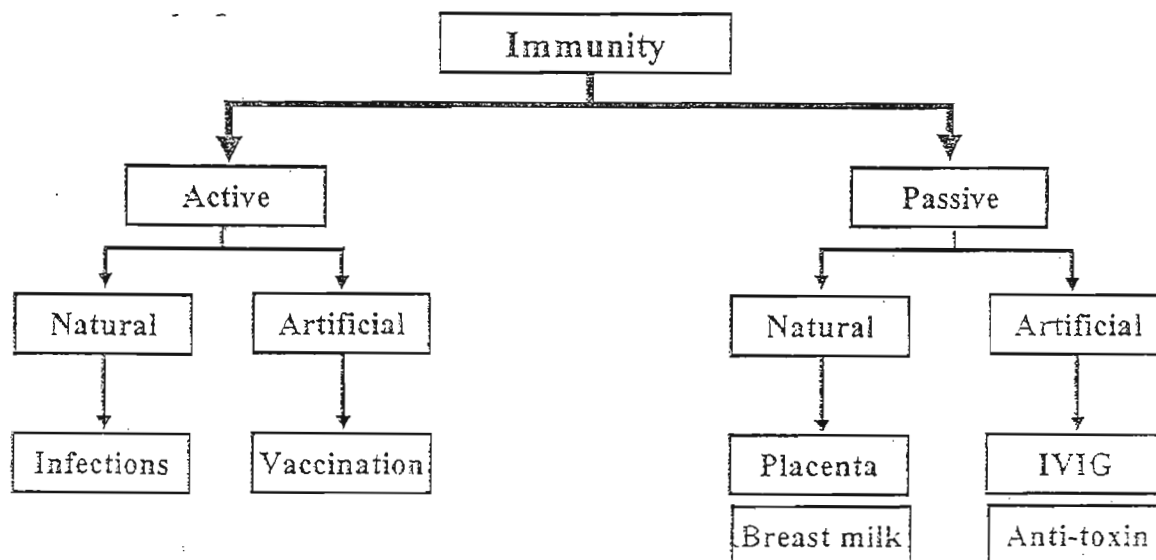
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- b. 7
- c. 15
- d. 22



# Immunization

## Classification



### A) Active Immunity

#### a. Natural

- ☑ Infections: Clinical or subclinical
  - Solid long-term immunity: Measles, Mumps, Rubella, Varicella
  - Transient short-term immunity: Influenza (Antigenic shift & drift)
  - Polioviruses: Lifelong immunity for each type, however, there is No cross immunity between the 3 types of polioviruses

#### b. Artificial

- ☑ Vaccination: Administration of vaccines or toxoids for prevention of diseases
  - Vaccines: Part of the pathogen used to produce specific immunity
  - Toxoids: Toxin with lost toxicity & retained antigenicity

### B) Passive Immunity

#### a. Natural

- ☑ Placenta: Transplacental passage of antibodies (IgG). Protective for 3-6 months
- ☑ Breast milk: IgA

#### b. Artificial

- ☑ Antitoxin: Diphtheria & tetanus (TIG & TAT)
- ☑ Immune globulin for measles
- ☑ Immune globulin for rubella
- ☑ VZIG
- ☑ Hepatitis A Immunoglobulin (IG)
- ☑ IVIG

No transplacental immunity to pertussis (IgM)

## Types of Vaccines

1. Killed (Inactivated): Salk (IPV), Hepatitis A
2. Living attenuated: Sabin (OPV), MMR, BCG, Varicella, Influenza
3. Toxoids: Diphtheria, Tetanus
4. Bacterial fraction: Capsular polysaccharide (Hemophilus influenza, meningococcal, pneumococcal vaccines), acellular pertussis
5. Recombinant vaccines: Hepatitis B

## Compulsory Vaccines in Egypt

Age	Vaccine	Type	Dose
1 <sup>st</sup> 3 months	▪ BCG	Live attenuated	0.05 ml ID
2 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
4 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
6 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
9 months	▪ OPV	Live attenuated	▪ 2 drops PO
12 months	▪ MMR	Live attenuated	▪ 0.5 ml SC
18 months	▪ OPV ▪ DPT ▪ MMR	Live attenuated D&T=toxoid, P=inactivated Live attenuated	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml SC
4-6 years	▪ OPV ▪ DT ▪ MMR	Live attenuated Toxoid Live attenuated	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml SC

## Non-Compulsory Vaccines

1. Hemophilus influenza vaccine
2. Pneumococcal vaccine
3. Meningococcal vaccine
4. Hepatitis A vaccine
5. Varicella vaccine
6. Rota vaccine
7. Influenza vaccine
8. Rabies vaccine

### General Contraindications to Vaccination

1. Serious allergic reaction e.g., anaphylaxis after a previous vaccine dose
2. Allergy to vaccine components
3. Moderate or severe acute illness with or without fever
4. Immunodeficiency: Live-attenuated vaccines; Sabin (OPV), MMR, BCG, Varicella
5. Immunosuppressive drugs: Live-attenuated vaccines...
6. Pregnancy: Live-attenuated vaccines

### Vaccines can be administered in

1. Mild acute illness with or without fever
2. Mild or moderate local reaction or fever after previous vaccine
3. Current antimicrobial therapy

### **Remember**

- **Bacterial Vaccines:** BCG, Hemophilus influenza, Pneumococcal, Meningococcal, Typhoid
- **Viral Vaccines:** OPV, MMR, Hepatitis B, Hepatitis A, Varicella, Rota, Rabies, Yellow fever

# Vaccines

	Oral Polio Vaccine ( <u>Sabin</u> )	Inactivated Polio Vaccine ( <u>Salk</u> )	DPT	Hepatitis B Vaccine
<b>Nature</b>	Live-attenuated	Inactivated (Killed)	Toxoids (D & T) + Killed whole cell pertussis	Recombinant DNA vaccine
<b>Against</b>	Poliovirus (3 strains)	Poliovirus (3 strains)	D-P-T	HBV
<b>Dose</b>	2 drops	0.5 ml	0.5 ml	0.5 ml
<b>Route</b>	Oral	IM	IM	IM
<b>Schedule</b>	<ul style="list-style-type: none"> <li>2, 4, 6, 9 months</li> <li>Boosters: 18 months &amp; 4-6 yrs</li> </ul>	<ul style="list-style-type: none"> <li>2, 4, 6 months</li> <li>Boosters: 18 months &amp; 4-6 yrs</li> </ul>	<ul style="list-style-type: none"> <li>2, 4, 6 months</li> <li>1<sup>st</sup> Booster: 18 months</li> <li>2<sup>nd</sup> Booster: 4-6 yrs (DT)</li> </ul>	<ul style="list-style-type: none"> <li>0, 1, 6 months (WHO)</li> <li>2, 4, 6 months (Egypt), why?</li> </ul>
<b>Precautions</b>	Cold chain Breast/feeding? (No significant reduction of immune response)			
<b>Advantages</b>	<input checked="" type="checkbox"/> Cheap <input checked="" type="checkbox"/> Gives <u>local</u> GIT & <u>systemic</u> humoral immunity <input checked="" type="checkbox"/> Effective (95%)	<input checked="" type="checkbox"/> No risk of VAPP	<input checked="" type="checkbox"/> Effective	<input checked="" type="checkbox"/> Effective (95%)
<b>Disadvantages</b>	Easily inactivated (Cold chain)	No local GIT immunity		
<b>Contra-indications (+ General CI)</b>	<input checked="" type="checkbox"/> Immunocompromised patients <input checked="" type="checkbox"/> Healthy household contacts of immunocompromised patients		<input checked="" type="checkbox"/> Children > 6 yrs <input checked="" type="checkbox"/> Neurological conditions <input checked="" type="checkbox"/> Convulsions or high fever after previous DPT dose	
<b>Side effects</b>	<input checked="" type="checkbox"/> Vaccine-associated paralytic poliomyelitis (= VAPP) is very rare (1 every 2 millions) <input checked="" type="checkbox"/> Loose stools	<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Mild fever	<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Fever <input checked="" type="checkbox"/> Convulsions	<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Fever

	Measles vaccine		MMR	BCG	Hemophilus influenza type b (Hib)
<b>Nature</b>	Live-attenuated		Live-attenuated	Live-attenuated	Polysaccharide vaccine
<b>Against</b>	Measles virus		M-M-R	TB bacilli	Hib
<b>Dose</b>	0.5 ml		0.5 ml	0.05 ml	0.5 ml
<b>Route</b>	SC		SC	Intra-dermal (Lt deltoid area)	IM
<b>Schedule</b>	<ul style="list-style-type: none"> <li>9 months</li> <li>Booster: as MMR (15 months)</li> <li>Booster: as MMR (4-6 yrs)</li> </ul>		<ul style="list-style-type: none"> <li>1<sup>st</sup> dose: 12-15 months</li> <li>2<sup>nd</sup> dose: at 18 months (or later at 4-6 yrs)</li> </ul>	<ul style="list-style-type: none"> <li>At birth or 1<sup>st</sup> 3 months</li> <li>Booster: 5 &amp; 11 yrs</li> </ul>	<ul style="list-style-type: none"> <li>2, 4, 6 months</li> <li>Booster: 12-15 month</li> </ul>
<b>Precautions</b>				<b>Tuberculin test</b> is indicated if the vaccine is given beyond 6-12 months of age	
<b>Advantages</b>	<input checked="" type="checkbox"/> Effective (95%) <input checked="" type="checkbox"/> Post-exposure prophylaxis: within 3 days after exposure		<input checked="" type="checkbox"/> Effective (99% after 2 <sup>nd</sup> dose)	<input checked="" type="checkbox"/> The only available vaccine for TB <input checked="" type="checkbox"/> ↓↓ Pulmonary TB (≈ 50% effectiveness) <input checked="" type="checkbox"/> ↓↓ TB meningitis & disseminated disease (≈ 50-80% effectiveness)	<input checked="" type="checkbox"/> Effective in prevention of meningitis, epiglottitis...
<b>Contra-indications (+ General CI)</b>	<input checked="" type="checkbox"/> Immunocompromised <input checked="" type="checkbox"/> Pregnancy or expected pregnancy (within 3 ms) <input checked="" type="checkbox"/> TB <input checked="" type="checkbox"/> Age < 8 months		<input checked="" type="checkbox"/> Immunocompromised <input checked="" type="checkbox"/> Pregnancy or expected pregnancy (within 3 ms) <input checked="" type="checkbox"/> TB <input checked="" type="checkbox"/> Age < 12 months	<input checked="" type="checkbox"/> Immunocompromised <input checked="" type="checkbox"/> Pregnancy	
<b>Side effects</b>	<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Fever		<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Fever <input checked="" type="checkbox"/> Arthritis	<input checked="" type="checkbox"/> Erythema, papule ± ulceration in 3-6 wks <input checked="" type="checkbox"/> Scar formation: 2-6 months <input checked="" type="checkbox"/> Regional LN: Anti-TB Rx may be needed <input checked="" type="checkbox"/> Disseminated infections: in immunocompromised individuals	<input checked="" type="checkbox"/> Local: Pain & redness <input checked="" type="checkbox"/> Systemic: Fever





	Meningococcal vaccine	Pneumococcal Conjugate Vaccine (PCV)	Pneumococcal Polysaccharide Vaccine (PPV)	Hemophilus influenza type b (Hib)
<b>Nature</b>	Polysaccharide vaccine	Polysaccharide vaccine	Polysaccharide vaccine	Polysaccharide vaccine
<b>Against</b>	A, C, Y, W135	7 types of bacteria (Heptavalent)	23 types of bacteria	Hib
<b>Route</b>	SC (0.5 ml)	IM (0.5 ml)	IM (0.5 ml)	IM (0.5 ml)
<b>Schedule</b>	<ul style="list-style-type: none"> <li>Single dose</li> <li>&gt; 2 yrs of age</li> <li>Protection for 2-3 yrs</li> <li>Protection starts after 10 days</li> </ul>	<ul style="list-style-type: none"> <li>2-6 months                             <ul style="list-style-type: none"> <li>3 doses: 2, 4, 6 months</li> <li>4<sup>th</sup> dose: 12-15 month</li> </ul> </li> <li>6-12 months                             <ul style="list-style-type: none"> <li>2 doses: with 2 ms interval</li> <li>3<sup>rd</sup> dose &gt; 12 months</li> </ul> </li> <li>12-24 months                             <ul style="list-style-type: none"> <li>2 doses with 2 ms interval</li> </ul> </li> <li>2-5 yrs: One dose</li> <li>&gt; 5 yrs: Not needed</li> </ul>	<ul style="list-style-type: none"> <li>Single dose</li> <li>&gt; 2 yrs of age</li> <li>Protection for 2-3 yrs</li> <li>Protection starts after 10 days interval</li> <li>2-5 yrs: One dose</li> <li>&gt; 5 yrs: Not needed</li> </ul>	<ul style="list-style-type: none"> <li>2-6 months                             <ul style="list-style-type: none"> <li>3 doses: 2, 4, 6 months</li> <li>Booster: 12-15 month</li> </ul> </li> <li>6-12 months                             <ul style="list-style-type: none"> <li>2 doses: with 2 ms interval</li> <li>Booster &gt; 12 months</li> </ul> </li> <li>12-24 months                             <ul style="list-style-type: none"> <li>1 + booster (2 ms interval)</li> </ul> </li> <li>2-5 yrs: One dose (Only)</li> <li>&gt; 5 yrs: Not needed</li> </ul>
<b>Indications</b>	<ul style="list-style-type: none"> <li>Epidemics</li> <li>Before splenectomy</li> <li>Sickle cell anemia</li> <li>Complement deficiency</li> </ul>	<ul style="list-style-type: none"> <li>All children &lt; 2 yrs (Routine)</li> <li>Children 2-5 yrs (Not immunized)                             <ul style="list-style-type: none"> <li>Before splenectomy</li> <li>Sickle cell anemia</li> <li>Complement deficiency</li> <li>Immunosuppressives</li> <li>Heart or lung diseases</li> <li>NS, CRF</li> <li>AIDS</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Children &gt; 2 yrs                             <ul style="list-style-type: none"> <li>Before splenectomy</li> <li>Sickle cell anemia</li> <li>Complement deficiency</li> <li>Immunosuppressives</li> <li>Heart or lung diseases</li> <li>NS, CRF</li> <li>AIDS</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>All children &lt; 2 yrs (Routine)</li> </ul>
<b>Side effects</b>	<ul style="list-style-type: none"> <li>Local: Pain &amp; redness</li> <li>Systemic: fever</li> </ul>	<ul style="list-style-type: none"> <li>Local: Pain &amp; redness</li> <li>Systemic: Fever</li> </ul>	<ul style="list-style-type: none"> <li>Local: Pain &amp; redness</li> <li>Systemic: Fever</li> </ul>	<ul style="list-style-type: none"> <li>Local: Pain &amp; redness</li> <li>Systemic: Fever</li> </ul>

# Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2008

For those who fall behind or start late, see the catch-up schedule

Vaccine	Age	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B <sup>1</sup>	HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB
Rotavirus <sup>2</sup>	RV		RV	RV	RV	RV						
Diphtheria, Tetanus, Pertussis <sup>3</sup>	DTaP		DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP
Haemophilus influenzae type b <sup>4</sup>	Hib		Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib
Pneumococcal <sup>5</sup>	PCV		PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV
Inactivated Poliovirus	IPV		IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV
Influenza <sup>6</sup>	Influenza (Yearly)											
Measles, Mumps, Rubella <sup>7</sup>	MMR						MMR		MMR	MMR	MMR	MMR
Varicella <sup>8</sup>	Varicella						Varicella		Varicella	Varicella	Varicella	Varicella
Hepatitis A <sup>9</sup>	HepA (2 doses)						HepA (2 doses)		HepA (2 doses)	HepA (2 doses)	HepA (2 doses)	HepA (2 doses)
Meningococcal <sup>10</sup>	MenACWY											

Range of recommended ages

Certain high-risk groups

This schedule includes the recommended age for routine administration of vaccine. Licensee notices, as of December 1, 2008, for children aged through 6 years. The dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Live, attenuated vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated, if approved by the Food and Drug Administration for that dose of

the series. Providers should consult the national Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: <http://www.cdc.gov/vaccines/imz/pubs/psp-list.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

## Hepatitis B vaccine (HepB). (Minimum age: birth)

- At birth:
  - Administer monovalent HepB to all newborns before hospital discharge.
  - If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
  - If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

### After the birth dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. The final dose should be administered no earlier than age 24 weeks.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).

### 4-month dose:

- Administration of 4 doses of HepB to infants is permissible when combination vaccines containing HepB are administered after the birth dose.

## Rotavirus vaccine (RV). (Minimum age: 6 weeks)

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 3 months 0 days.
- If Rotarix<sup>®</sup> is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

## Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). (Minimum age: 6 weeks)

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4 through 6 years.

## Haemophilus influenzae type b conjugate vaccine (Hib). (Minimum age: 6 weeks)

- PRP-OMP (Proventis<sup>®</sup> or Comvax<sup>®</sup> HepB-Hib) is administered at ages 2 and 4 months; a dose at age 6 months is not indicated.
- DTaP/DTaP/Hib should not be used for doses at ages 2, 4, or 6 months but can be used as the first dose in children aged 12 months or older.

## Pneumococcal vaccine. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

- PCV is recommended for all children aged younger than 6 years.
- Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.

- Administer PPSV to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-8]), including a cochlear implant.

## 6. Influenza vaccine. (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])

- Administer annually to children aged 6 months through 13 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 mL if aged 3 years or older.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

## 7. Measles, mumps, and rubella vaccine (MMR). (Minimum age: 12 months)

- Administer the second dose at age 4 through 5 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.

## 3. Varicella vaccine. (Minimum age: 12 months)

- Administer the second dose at age 4 through 5 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.

## 9. Hepatitis A vaccine (HepA). (Minimum age: 12 months)

- Administer to all children aged 1 year (i.e., aged 12 through 23 months).
- Administer 2 doses at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA also is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55[No. RR-7].

## 10. Meningococcal vaccine. (Minimum age: 2 years for meningococcal conjugate vaccine [MCV] and for meningococcal polysaccharide vaccine [MPSV])

- Administer MCV to children aged 2 through 16 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other high-risk groups. See *MMWR* 2005;54[No. RR-7].
- Persons who received MPSV 3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV.

The Recommended Immunization Schedule for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices ([www.cdc.gov/vaccines/recs/acip](http://www.cdc.gov/vaccines/recs/acip)), the American Academy of Pediatrics (<http://www.aap.org>), and the American Academy of Family Physicians (<http://www.aafp.org>).

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# Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2009

For those who fall behind or start late, see the schedule below and the catch-up schedule

Vaccine ▽	Age ►	7–10 years	11–12 years	13–18 years	
Tetanus, Diphtheria, Pertussis <sup>1</sup>		see footnote 1	Tdap	Tdap	Range of recommended ages
Human Papillomavirus <sup>2</sup>		see footnote 2	HPV (3 doses)	HPV Series	
Meningococcal <sup>3</sup>		MCV	MCV	MCV	Catch-up immunization
Influenza <sup>4</sup>			Influenza (Yearly)		
Pneumococcal <sup>5</sup>			PPSV		Certain high-risk groups
Hepatitis A <sup>6</sup>			HepA Series		
Hepatitis B <sup>7</sup>			HepB Series		
Inactivated Poliovirus <sup>8</sup>			IPV Series		
Measles, Mumps, Rubella <sup>9</sup>			MMR Series		
Varicella <sup>10</sup>			Varicella Series		

The schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 7 through 18 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated. If approved by the Food and Drug Administration for that dose of

the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: <http://www.cdc.gov/vaccines/pubs/acip-list.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

- Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).** (Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL®)  
Administer at age 11 or 12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoid (Td) booster dose.  
• Persons aged 13 through 18 years who have not received Tdap should receive a dose.  
A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose; however, a shorter interval may be used if pertussis immunity is needed.
- Human papillomavirus vaccine (HPV).** (Minimum age: 9 years)  
Administer the first dose to females at age 11 or 12 years.  
Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).  
Administer the series to females at age 13 through 18 years if not previously vaccinated.
- Meningococcal conjugate vaccine (MCV).**  
Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.  
• Administer to previously unvaccinated college freshmen living in a dormitory.  
MCV is recommended for children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other groups at high risk. See *MMWR* 2005;54(No. RR-7).  
Persons who received MPSV 5 or more years previously and remain at increased risk for meningococcal disease should be revaccinated with MCV.
- Influenza vaccine.**  
Administer annually to children aged 6 months through 18 years.  
For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.  
• Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

- Pneumococcal polysaccharide vaccine (PPSV).**  
• Administer to children with certain underlying medical conditions (see *MMWR* 1997;46(No. RR-8)), including a cochlear implant. A single revaccination should be administered to children with functional or anatomic asplenia or other immunocompromising condition after 5 years.
- Hepatitis A vaccine (HepA).**  
• Administer 2 doses at least 6 months apart.  
• HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).
- Hepatitis B vaccine (HepB).**  
• Administer the 3-dose series to those not previously vaccinated.  
• A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.
- Inactivated poliovirus vaccine (IPV).**  
• For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.  
• If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
- Measles, mumps, and rubella vaccine (MMR).**  
• If not previously vaccinated, administer 2 doses or the second dose for those who have received only 1 dose, with at least 28 days between doses.
- Varicella vaccine.**  
• For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56(No. RR-4)), administer 2 doses if not previously vaccinated or the second dose if they have received only 1 dose.  
• For persons aged 7 through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.  
• For persons aged 13 years and older, the minimum interval between doses is 28 days.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices ([www.cdc.gov/vaccines/recs/acip/](http://www.cdc.gov/vaccines/recs/acip/)), the American Academy of Pediatrics (<http://www.aap.org/>), and the American Academy of Family Physicians (<http://www.aafp.org/>).

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# Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 2009

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Rotavirus <sup>2</sup>	6 wks	4 weeks	4 weeks <sup>2</sup>		
Diphtheria, Tetanus, Pertussis <sup>3</sup>	6 wks	4 weeks	4 weeks	6 months	6 months <sup>3</sup>
<i>Haemophilus influenzae</i> type b <sup>4</sup>	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12–14 months No further doses needed if first dose administered at age 15 months or older	4 weeks <sup>4</sup> if current age is younger than 12 months 3 weeks (as final dose) <sup>4</sup> if current age is 12 months or older and second dose administered at younger than age 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal <sup>5</sup>	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for high-risk children who received 3 doses at any age	
Inactivated Poliovirus <sup>6</sup>	6 wks	4 weeks	4 weeks	4 weeks <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	3 months			
Hepatitis A <sup>9</sup>	12 mos	6 months			

CATCH-UP SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis <sup>10</sup>	7 yrs <sup>10</sup>	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at age 12 months or older	6 months if first dose administered at younger than age 12 months	
Human Papillomavirus <sup>11</sup>	9 yrs	Routine dosing intervals are recommended <sup>11</sup>			
Hepatitis A <sup>9</sup>	12 mos	6 months			
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated Poliovirus <sup>6</sup>	6 wks	4 weeks	4 weeks	4 weeks <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	3 months if the person is younger than age 13 years 4 weeks if the person is aged 13 years or older			

- Hepatitis B vaccine (HepB).**
  - Administer the 3-dose series to those not previously vaccinated.
  - A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB<sup>®</sup> is licensed for children aged 11 through 15 years.
- Rotavirus vaccine (RV).**
  - The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
  - Administer the final dose in the series by age 3 months 0 days.
  - If Rotarix<sup>®</sup> was administered for the first and second doses, a third dose is not indicated.
- Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).**
  - The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.
- Haemophilus influenzae* type b conjugate vaccine (Hib).**
  - Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy; administering 1 dose of Hib vaccine to these persons is not contraindicated.
  - If the first 2 doses were PRP-OMP (PedvaxHIB<sup>®</sup> or Comvax<sup>®</sup>), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
  - If the first dose was administered at age 7 through 11 months, administer 2 doses separated by 4 weeks and a final dose at age 12 through 15 months.
- Pneumococcal vaccine.**
  - Administer 1 dose of pneumococcal conjugate vaccine (PCV) to all healthy children aged 24 through 59 months who have not received at least 1 dose of PCV on or after age 12 months.
  - For children aged 24 through 59 months with underlying medical conditions, administer 1 dose of PCV if 3 doses were received previously or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses were received previously.
  - Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions [see MMWR 2000;49(No. RR-9)], including a cochlear implant, at least 8 weeks after the last dose of PCV.
- Inactivated poliovirus vaccine (IPV).**
  - For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
  - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
- Measles, mumps, and rubella vaccine (MMR).**
  - Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
  - If not previously vaccinated, administer 2 doses with at least 28 days between doses.
- Varicella vaccine.**
  - Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
  - For persons aged 12 months through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
  - For persons aged 13 years and older, the minimum interval between doses is 28 days.
- Hepatitis A vaccine (HepA).**
  - HepA is recommended for children older than 1 year who live in areas where vaccination program target older children or who are at increased risk of infection. See MMWR 2006;55(No. RR-7).
- Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).**
  - Doses of DTaP are counted as part of the Td/Tdap series.
  - Tdap should be substituted for a single dose of Td in the catch-up series or as a booster for child aged 10 through 18 years; use Td for other doses.
- Human papillomavirus vaccine (HPV).**
  - Administer the series to females at age 13 through 18 years if not previously vaccinated.
  - Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 2 and 6 months after the first dose). However, the minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be given at least 24 weeks after the first dose.



# Nutritional Disorders

## Classification

Pediatric nutritional disorders can be classified into:

- A) Severe childhood undernutrition (Protein-energy malnutrition)
- B) Overweight & obesity
- C) Specific vitamin & mineral deficiency: e.g., iron, vitamin D & A deficiency

## Protein-Energy Malnutrition

### Definition

- Group of related disorders characterized by protein & energy deficiency
- PEM is almost always associated with other nutritional deficiencies, therefore the term "severe childhood undernutrition" is preferred
- They have variable clinical & biochemical presentations (but overlap may occur)

### Contributing factors to PEM

1. Poverty, Ignorance, Illiteracy
2. Infection: Recurrent GE, measles, TB...
3. Urbanization
4. Disasters
  - Natural: Earthquakes
  - Human-related: Wars
5. Environmental degradation

### Clinical Spectrum

	Definition	Features
Marasmus	Severe form of chronic undernutrition	Wasting
Kwashiorkor	Severe form of chronic protein deficiency	Edema
Marasmic-KWO	Mixed marasmus & Kwashiorkor	Wasting + Edema
Mixed forms	Mixed	Mixed

**NB: Nutritional dwarfism** Mild to moderate form of chronic undernutrition  
 Short stature & Underweight (No wasting & No edema)  
 Commonest form of undernutrition (Recurrent infections)

### Remember

#### Main Features



Marasmus



Kwashiorkor

# Kwashiorkor

## Definition

- Severe form of chronic malnutrition caused by protein deficiency with adequate caloric intake in the form of excess CHO

## Incidence

- 6 months-2 years (Age of weaning)

## Etiology

### A) Dietetic

- ☑ Wrong compensation of scanty breast milk or over-diluted formula by excess CHO
- ☑ Weaning: Substitution of milk with high CHO diet (without proteins) e.g., potatoes, rice water, starch...

### B) Infections

- ☑ Post-GE: anorexia, vomiting, diarrhea, wrong dietary restriction
- ☑ Post-measles

### C) Maternal deprivation

## Clinical Picture

4 Constant

### A) Constant manifestations

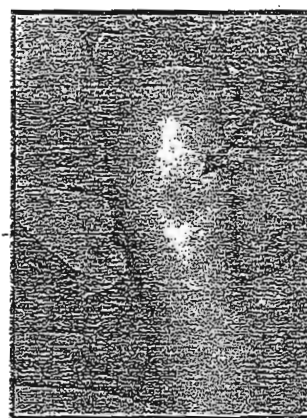
#### 1. Edema (Diagnosis can not be made in absence of edema)

##### ☑ Cause:

- Hypoalbuminemia ( $\downarrow\downarrow$  Oncotic pressure)
- $\uparrow\uparrow$  ADH & aldosterone (try to  $\downarrow\downarrow$  effective plasma volume)

##### ☑ C/P

- Site of onset: Dorsum of the feet
- March: Then becomes generalized;
  - LL edema
  - Dorsum of hands
  - No Ascites
- Character: Pitting



Pitting Edema

#### 2. Mental changes

##### ☑ Cause:

- $\downarrow\downarrow$  Amino acids (Neurotransmitters)
- $\downarrow\downarrow$  Niacin (& NAD, NADP)
- Maternal deprivation

##### ☑ Manifestations

- Apathy
- Lethargy
- Disinterested in the surroundings
- Miserable
- No mental retardation (These changes are reversible with Rx)



Apathy

#### 3. Disturbed muscle/fat ratio

- Muscle: Wasting ( $\downarrow\downarrow$  Proteins)
- Fat: Excess SC fat ( $\uparrow\uparrow$  CHO)

Skin fold thickness

#### 4. Growth failure: Detected by skin fold thickness (May be masked by edema & excess SC fat)



## B). Variable manifestations

7 Variable

### 1. Hair changes

#### ☑ Cause:

- ↓↓ Sulfur-containing amino acid
- ↓↓ Tyrosine (↓↓ Melanin)
- ↓↓ Copper

#### ☑ Manifestations

- Sparse, soft & easily detached
- Light in color
- Flag sign: With recovery (Alternating light & dark bands)

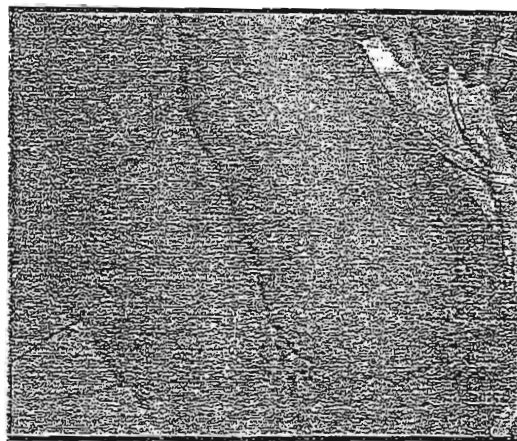
### 2. Skin changes

#### ☑ Cause:

- ↓↓ Vitamin A
- ↓↓ Zinc
- ↓↓ Niacin
- Disturbed amino acid metabolism

#### ☑ Manifestations

- Site: Buttocks, perineum
- Lesions: Cracking, fissuring, ulceration, hypo- & hyperpigmentation ± infection



### 3. Hepatomegaly

#### ☑ Cause:

- Accumulation of fat & glycogen

#### ☑ Manifestations

- Liver: Enlarged & soft

#### Remember

- Hepatomegaly is Variable
- Fatty infiltration is Constant

### 4. GIT

- a. Anorexia: Mental changes & infection
- b. Vomiting: GE
- c. Diarrhea: Mucosal damage, GE

### 5. Vitamin deficiency

- a. Vitamin A: Keratomalacia, xerophthalmia, blindness, bitot spots, infections
- b. Vitamin B: Stomatitis & glossitis
- c. Vitamin C: Scurvy
- d. Vitamin K: Bleeding (Hypoprothrombinemia)
- e. Vitamin D: Rickets does not occur (*Rickets is a disease of growing bones*)

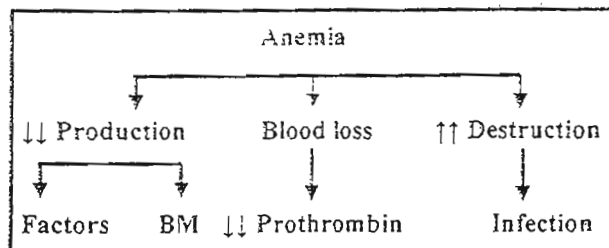
### 6. Infections

- a. Gastroenteritis (GE)
- b. Bronchopneumonia
- c. Skin infection
- d. Septicemia

### 7. Anemia (See Hematology) ➡

## Complications

1. Infection: Pneumonia, GE...
2. Hypothermia & Hypoglycemia
3. Bleeding
4. Shock: Hypovolemic or septic



## Investigations

### A) Laboratory

- CBC: Anemia, leukocytosis (Infection)
- Serum albumin:  $\downarrow\downarrow$  (N = 3.5-5.5 g/dl)
- Serum globulins:  $\downarrow\downarrow$   $\alpha$  &  $\beta$ -globulins ( $\uparrow\uparrow$   $\gamma$ -globulins due to infections)
- Dilutional hyponatremia
- Hypokalemia
- Hypoglycemia (Due to disturbed glucose metabolism)

Total body Na is  $\uparrow\uparrow$

### B) Imaging

- CXR: Pneumonia

## Differential Diagnosis

### 1. Other causes of generalized edema

	Mechanism	C/P
Nephrotic	Hypoalbuminemia ( $\downarrow\downarrow$ OP)	Nephrotic syndrome (Describe)
Nutritional	Hypoalbuminemia ( $\downarrow\downarrow$ OP)	Kwashiorkor (Ascites is very rare)
Hepatic	Hypoalbuminemia ( $\downarrow\downarrow$ OP)	Jaundice, hepatomegaly...
Cardiac	$\uparrow\uparrow$ Venous pressure	Tachycardia, Tachypnea, Tender hepatomegaly
Allergic	$\uparrow\uparrow$ Capillary permeability	History (exposure) + Itching - Urticaria (wheals)

### 2. Skin diseases:

- a. Pellagra: 3Ds (Dermatitis, Dementia, Diarrhea)
- b. Diaper dermatitis

### 3. Other causes of PEM: See classification table

#### a. Marasmus

#### b. Marasmic- Kwashiorkor

##### ☒ Etiology

- Kwashiorkor patient: with CHO restriction
- Marasmic patient: treated with CHO diet (without adequate proteins)

##### ☒ C/P

- Kwashiorkor patient (Edema) + Loss of SC tissue
- Marasmic patient (Wasting) + Edema

Wasting + Edema

#### c. Nutritional dwarfism (Most common form of childhood undernutrition)

- Mild to moderate form of chronic undernutrition
- Short stature, Underweight & Recurrent infections (No wasting & No edema)

## Prevention

1. General measures: Environmental sanitation, Socioeconomic development  
Adequate food supply, prevention of infection
2. Promotion of breastfeeding: It is the simplest, cheapest & most effective method
3. Health education
4. Nutritional education: Value of breastfeeding, proper weaning...
5. Regular assessment of child health & growth pattern: Growth curves
6. Regular assessment of nutritional state: Early manifestations of nutritional disorders
7. Proper management of childhood infections: Especially GE...
8. Proper antenatal care

# Marasmus

## Definition

- Severe form of chronic malnutrition caused by **insufficient caloric intake**

## Incidence

- Nutritional marasmus: 6 months-2 years
- Non-nutritional marasmus: Depends on the etiology

## Etiology (↓↓ Calories)

### A) Nutritional marasmus

- ☒ Dietetic
  - Scanty breast milk
  - Over-diluted formula
- ☒ Infection (Recurrent GE):
  - ↓↓ Intake: Anorexia & vomiting
  - ↑↑ Losses: Diarrhea
  - Wrong medical advice

### B) Non-nutritional marasmus

- CVS: CHD, RHD
- Resp.: TB, Cystic fibrosis
- Renal: CRF, RTA
- Others: Cleft palate, CHPS, malignancy, starvation, anorexia nervosa
- Hepatic: Chronic liver disease (Cirrhosis)
- Blood: Chronic hemolytic anemia
- GIT: Malabsorption (Parasites, Celiac...)



## Clinical Picture

- A) Loss of weight: Growth curves (Quite below the expected weight for age i.e., < 5<sup>th</sup> %)
- B) Muscle wasting
- C) Loss of SC fat: Thin wrinkled skin with marked bony prominences

## Degrees of Marasmus

	Weight loss	Loss of SC fat
1 <sup>st</sup> degree	15-25% of the expected weight	Abdominal wall
2 <sup>nd</sup> degree	25-35% of the expected weight	Buttocks & thighs
3 <sup>rd</sup> degree	> 35% of the expected weight	Face (Senile facies)

- D) Vitamin deficiency: A, D, K, C, B (*See kwashiorkor for manifestations*)
- E) Mineral deficiency: Iron deficiency anemia
- F) Dehydration
- G) Other manifestations Hunger
  - Anxious look, irritability & crying (*DD: Kwashiorkor*)
  - Hunger diarrhea: Scanty dry greenish stools

## Investigations

- CBC: Anemia, leukocytosis (Infection)
- Serum proteins: Not markedly ↓↓
- Hypoglycemia
- Investigations of non-nutritional marasmus

## Complications

1. Infection: Pneumonia, GE...
2. Hypothermia & Hypoglycemia



2<sup>nd</sup> degree marasmus

# Management of PEM

## A) Hospital Management

### ☒ Indications

- Moderate or severe Kwashiorkor
- Marasmic kwashiorkor
- 3<sup>rd</sup> degree marasmus
- Complications

### ☒ Management plan (Stabilization & Rx of complications)

- Infection (GE, pneumonia...): Proper antibiotics
- Shock: Shock therapy (Lactated ringer's 20 ml/Kg over 1 hr), FFP can be used
- Dehydration: IV fluid therapy (Deficit therapy)
- Electrolyte disturbances: should be corrected
- Anemia: Packed RBCs
- Hypoglycemia
- Hypothermia: External heating

## B) Nutritional Management (Home or hospital)

	Marasmus	Kwashiorkor
Rational (Target)	↑↑ Calories 150-200 Kcal/Kg/day	↑↑ Proteins 4-6 gm/Kg/day
Type of foods	According to the age: <ul style="list-style-type: none"> <li>▪ Milk-fed: Milk (Lactose-free may be used initially) then standard...</li> <li>▪ Weaned infants: Balanced diet [CHO=50%, Lipids=35 %, Ptns=15%]</li> </ul>	According to the age: <ul style="list-style-type: none"> <li>▪ Milk-fed: Milk (Lactose-free may be used initially) then standard...</li> <li>▪ Weaned infants: High-protein diet <ul style="list-style-type: none"> <li>- Egg, meat, chicken, beans</li> <li>- Vegetables, fruits</li> </ul> </li> </ul>
Amount	Start with ≈ 75 Kcal/Kg/day ↑↑ Amount & concentration according to the child <b>tolerance</b> (Rate of ↑↑ ≈ 5-10 Kcal/Kg/day)	Start with ≈ 1 gm/Kg/day ↑↑ Amount & concentration according to the child <b>tolerance</b>
Route	Oral or Nasogastric tube	Oral or Nasogastric tube More difficult, why? Anorexia
Vitamins	➤ Vitamin A <ul style="list-style-type: none"> <li>- 6-12 months: 100.000 IU/day</li> <li>- &gt; 12 months: 200.000 IU/day</li> </ul> ➤ Vitamin B, C, D, Folic acid	
Minerals	➤ Iron (4-6 mg/kg/day) ➤ Potassium ➤ Zinc	

## Complications of Rx

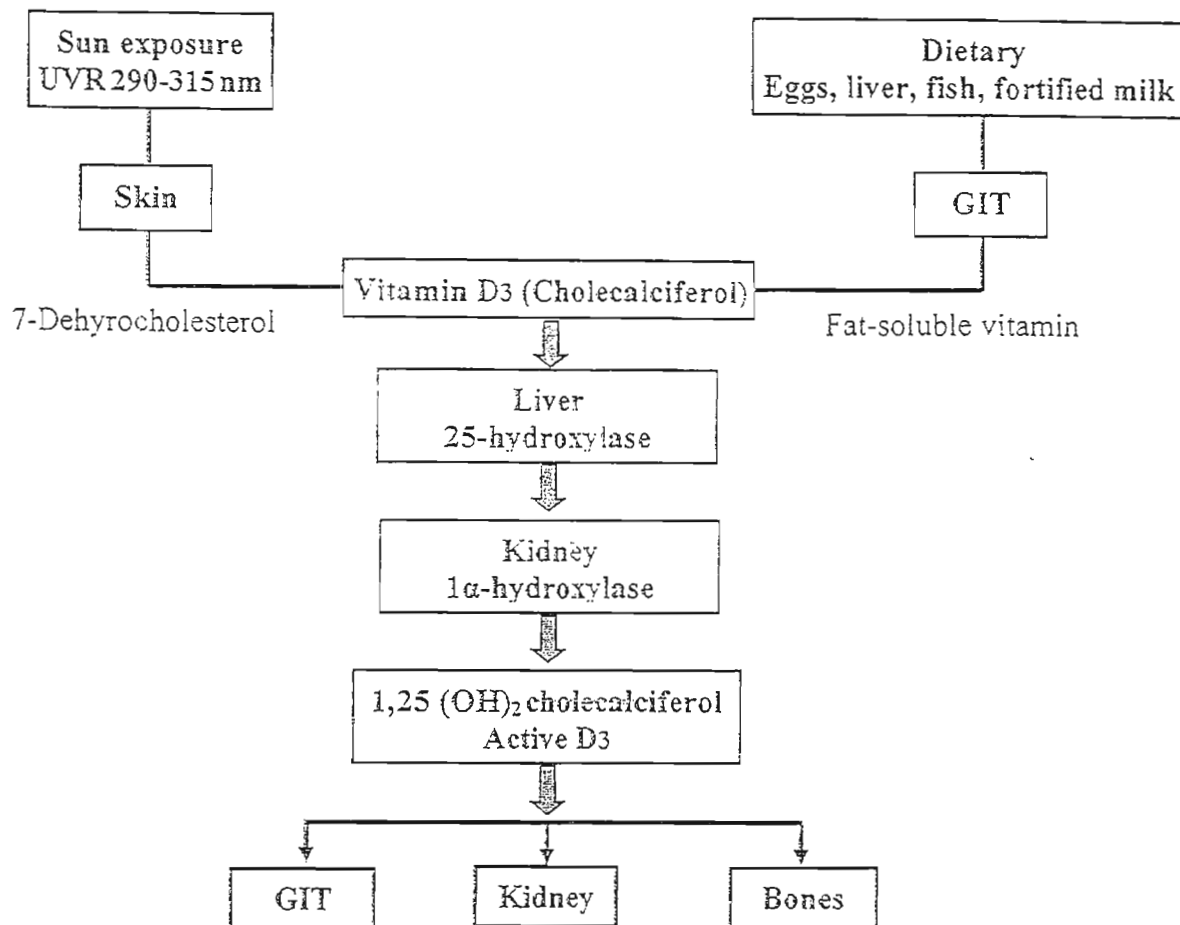
1. Diarrhea: Due to transient CHO intolerance (Lactose)
2. Nutritional recovery syndrome: Firm enlarged liver

# Rickets

## Definition

- Defective mineralization of the growing bones (Disease of childhood)

## Physiologic Considerations



## Hormonal Regulation of Ca Homeostasis

	Vitamin D	Parathyroid hormone
Intestine	↑↑ Ca absorption	↑↑ Ca absorption (through ↑↑ Vit. D)
Kidneys	↑↑ Ca reabsorption	↑↑ PO <sub>4</sub> excretion (Phosphaturia)
Bones	Normal mineralization of bones	Bone resorption (↑↑ Osteoclasts)

Structure of Normal Bone Formed of matrix (Osteoid tissue) & minerals (Ca & P)

Bone Layers (in the epiphyseal region)

1. Zone of resting cartilage: 1 layer
2. Zone of proliferating cartilage: 6-8 layers
3. Zone of degenerating cartilage (= Zone of provisional calcification): Deposition of Ca & P
4. Zone of ossification: Invasion of the ZPC by BV & osteoblasts with mineralization

Bone Pathology in Rickets Proliferation without degeneration

### **Remember**

- **Osteomalacia:** ↓↓ Mineralization of bones (any age)
- **Osteoporosis:** ↓↓ Bone volume & ↓↓ Bone minerals

## Types of Rickets (= Classification)

- A) Ca deficiency rickets with  $2ry \uparrow \uparrow$  PTH
  - Vitamin D deficiency
  - Malabsorption of vitamin D
  - Hepatic disease
  - Renal osteodystrophy
- B) Primary  $PO_4$  deficiency (No  $2ry \uparrow \uparrow$  PTH)
  - XL-D Hypophosphatemic rickets
  - Fanconi syndrome: PCT dysfunction [Glucosuria, phosphaturia, aminoaciduria]
- C) End-organ resistance to  $1,25 (OH)_2$
- D) Cases resembling rickets: Hypophosphatasia

## Another Classification

	Vitamin D deficiency rickets	Non-Vitamin D deficiency rickets
Incidence	More common	Less common
Age	6 months-2 years	Any age
Response to Vit D therapy	Good	Poor

## Vitamin D-Deficiency Rickets


### Definition

Defective mineralization of the growing bones (Disease of childhood)

### Incidence

- 6 months-2 years (Age of weaning)

### Etiology

- A) Lack of vitamin D
  - a. Inadequate intake of vitamin D
    - ☒ Prolonged exclusive breast milk
    - ☒ Rachitogenic diet 
  - b. Inadequate sun exposure
    - ☒ Wrapping
    - ☒ Winter-time
    - ☒ Windows

### **Remember**

Rachitogenic diet is any of:

- Deficient in vitamin D
- Deficient in Ca &  $PO_4$
- Non-optimum Ca:P ratio
- $\uparrow \uparrow$  Content of phytate or oxalates

B) Other causes: Malabsorption, renal or hepatic diseases

### Clinical Picture

#### A) Skeletal

##### 1. Head

- Frontal bossing
- Macrocephaly (Cranial cause)
- Delayed closure of AF
- Delayed dentition

NB: Craniotabes is Ping-Pong ball sensation detected on pressing over the occiput (= Bone thinning)



## 2. Limbs

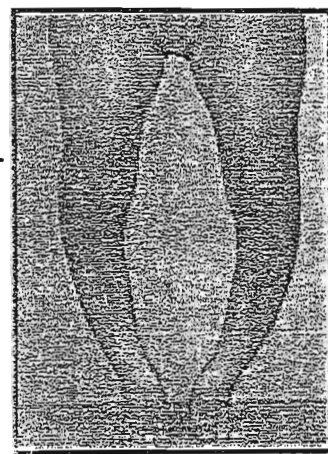
- Broadening of the ends of long bones
- Marfan sign: Transverse groove across medial malleolus
- Deformities of the UL: Convexity of the forearm (in creeping infants)
- Deformities of the LL
  - Genu varum: Bow legs
  - Genu valgum: Knock knees
  - Genu recurvatum: Overextension of the knees



Broadening (At the wrist)



Genu valgum



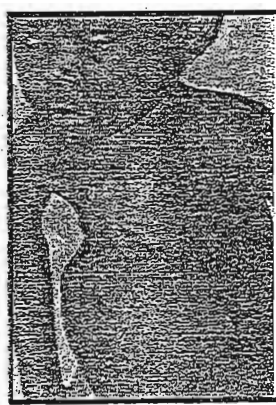
Genu varum

## 3. Chest

- Rosary beads: Cartilage proliferation at the costochondral junctions
- Pigeon chest: ↑↑ AP diameter of the chest (Protrusion of the sternum + rib flaring)
- Harrison sulcus: Horizontal groove along the costal insertion of the diaphragm
- Longitudinal sulcus: Vertical groove behind rosary beads



Rosary beads



Pigeon chest (Harrison sulcus)



Pigeon

## 4. Spine: Due to laxity of ligaments

- Kyphosis (Correctable) "DD: Pott's disease"
- Scoliosis
- Kyphoscoliosis
- Lumbar lordosis



## 5. Pelvis: Contracted pelvis (important in ♀)



B) Muscles & Ligaments: Hypotonia due to hypophosphatemia leading to:

1. Delayed motor milestones (Sitting, crawling, standing, walking...)
2. Downward displacement of liver & spleen (Visceroptosis)
3. Abdominal Distension due to:
  - Hypotonia
  - Visceroptosis (Not true enlargement)
  - Constipation

C) Neurological

1. Anorexia, Irritability, sweating
2. Hypocalcemic tetany:

a. Causes of hypocalcemia

- Parathyroid gland exhaustion
- Bone depletion (prolonged untreated cases)
- Vitamin D (IM massive dose) due to rapid mobilization of Ca from blood to bone

b. Manifestations

☑ Latent tetany (Serum Ca = 7-9 mg %)

Asymptomatic, only elicited by provocation

- Chvostek sign: Tapping of the Facial nerve → Twitches of facial muscles
- Trousseau sign: Constriction of the UL by sphygmomanometer (Carpal spasm)
- Peroneal sign: Tapping of the peroneal nerve → Pedal spasm

☑ Manifest tetany (Serum Ca < 7 mg %)

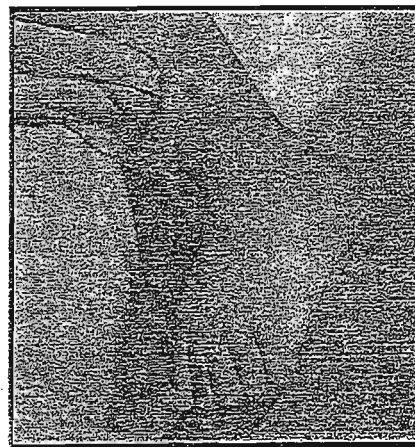
- Carpopedal spasm
- Laryngospasm
- Convulsions

### Remember

Ca is usually normal in rickets due to 2ry hyperparathyroidism



Carpal spasm



Pedal spasm

### Complications of Rickets

1. Respiratory: Chest infections, atelectasis (collapse), why?
2. Neurological: Tetany, convulsions, laryngospasm
3. Short stature (disproportionate)
4. Bone fractures & deformities
5. Iron deficiency anemia (Breast milk is deficient in both vitamin D & iron)
6. Contracted pelvis (Obstructed labor in ♀)
7. Complications of treatment (Vitamin D): Hypervitaminosis D

### Causes of chest infection:

- Hypotonia (weak cough)
- Chest deformities



## Differential Diagnosis

1. Delayed closure of anterior fontanel
2. Delayed Dentition

Delayed closure of A.F	Delayed Dentition
▪ Rickets	▪ Rickets
▪ Osteogenesis imperfecta	▪ Osteogenesis imperfecta
▪ Down syndrome	▪ Down syndrome
▪ Hypothyroidism	▪ Hypothyroidism
▪ Intracranial causes of macrocephaly	

### 3. Delayed walking

#### a. Neurological causes [Central & peripheral]

- Cerebral palsy
- Mental retardation
- Hydrocephalus
- Neuromuscular disorders
  - AHC: Werdnig-Hoffmann disease & Poliomyelitis
  - Nerve: Neuropathy (e.g., Guillain-Barré syndrome...)
  - Neuromuscular junction: Myasthenia gravis
  - Muscle: Myopathy

#### b. Bone: Rickets, trauma, fractures

#### c. Training: diagnosed by exclusion

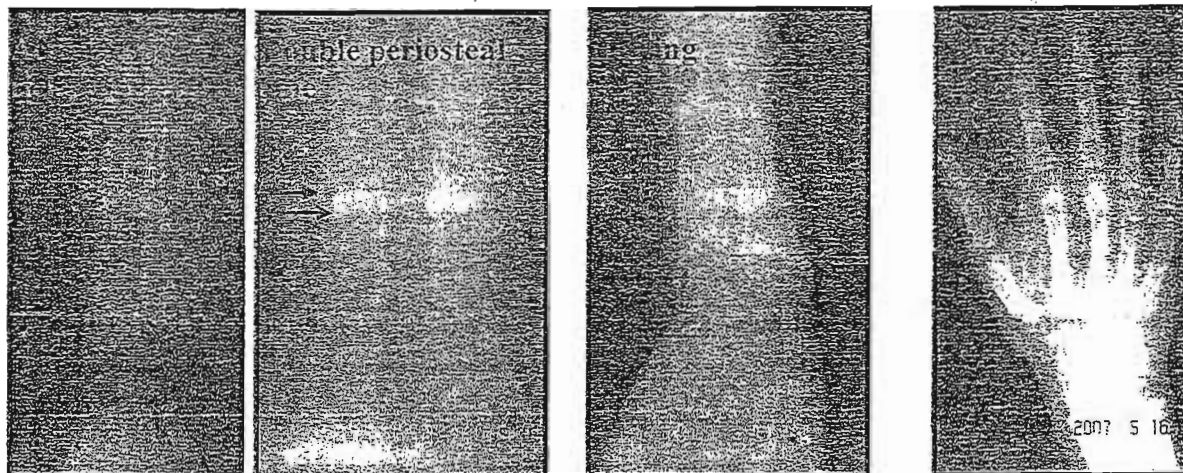
## Investigations

### A) Laboratory

- Serum calcium: Normal or ↓↓, When? (N = 9-11 mg/dl)
- Serum phosphorus: ↓↓ (N = 4.5-6.5 mg/dl)
- Serum alkaline phosphatase: ↑↑ (Early manifestation)

### B) Imaging (Radiological improvement start to occur after 2 wks of vitamin D therapy)

	Active	Healing	Healed
Metaphysis	Broadening, Cupping & Fraying	Dense <u>concave</u> white line of calcification	Dense <u>straight</u> white line of calcification
Diaphysis	↓↓ Bone density Fractures (Green-stick) Double periosteal line	Still there is manifestations of active rickets (but less severe)	Improved bone density
Epiphysis	↑↑ Joint space Bone age (Carpal bones)		



## Prevention

1. **Nutritional education:** Value of breastfeeding, proper weaning...
  - Diet rich in vitamin D: eggs, liver, oily fish, fortified milk
  - Avoid rachitogenic diet (*See before*)
2. **Vitamin D supplementation [40 IU = 1 µg]**
  - Full-term: 400-800 IU/day (as early as the 3<sup>rd</sup> month)
  - Preterm: 1000-1500 IU/day (as early as the 1<sup>st</sup> month)
3. **Sun exposure (UVR)**
4. **Regular assessment of nutritional state:** Early manifestations of rickets

## Treatment

### A) Vitamin D therapy

#### a. Oral therapy

- Dose
  - Vitamin D<sub>3</sub>: 3000-5000 IU/day
  - Active form of vitamin D: 0.5-2 µg/day (1-α preparation of Vit. D can be used)
- Duration: 2-4 weeks

#### b. Parenteral therapy

- Dose
  - Vitamin D<sub>3</sub>: 600.000 IU (Shock therapy)
- Duration: **Single IM dose**
- Advantages
  - More rapid
  - No need for parents compliance
  - Diagnosis of non-vitamin D deficiency rickets
- Disadvantages (Side effects)
  - Tetany
  - Hypervitaminosis D

Monitoring of HR is essential  
Stop if bradycardia occurs

### B) Treatment of complications

- a. **Tetany:** IV Ca gluconate 10% "1 ml/Kg" (Slowly while monitoring heart rate, why?)
- b. **Deformities & Fractures:** Orthopedic care (After complete bone healing)
- c. **Infections:** proper antibiotics
- d. **Iron deficiency anemia:** Iron (6 mg/Kg/day)

## Hypervitaminosis D

### Etiology

- Prolonged oral vitamin D therapy
- Parenteral vitamin D therapy (Shock therapy)

### Clinical Picture

- GIT: Anorexia, nausea, vomiting, constipation
- Renal: Polyuria, polydipsia, renal stones (Dysuria, colics, UTI...)

### Prevention Careful vitamin D therapy

### Investigations

- Laboratory: ↑↑ serum Ca, ↑↑ Urinary Ca
- Imaging: X-rays, US (Nephrocalcinosis, stones)

### Treatment

Stop vitamin D & Ca therapy, IV fluids, Steroids

# Non-Vitamin D Deficiency Rickets

## Classification

### A) Renal rickets

#### a. Renal glomerular

- CRF: Due to defective vitamin D activation ( $1\alpha$ -hydroxylation)
- CRF should be suspected in patients with non-nutritional rickets

#### b. Renal tubular

- Vitamin D resistant Hypophosphatemic rickets (XL-D)
- Vitamin D resistant Hypocalcemic rickets (Vitamin D dependent rickets)
- Fanconi syndrome: PCT dysfunction [Glucosuria, phosphaturia, aminoaciduria]
- Cystinosis: Fanconi syndrome + Corneal cystine crystal (*Pathognomonic*)
- Lowe syndrome: Oculo-cerebro-renal syndrome [Glaucoma & cataract-MR- Fanconi]
- Lightwood: Infantile renal tubular acidosis
- Lignac

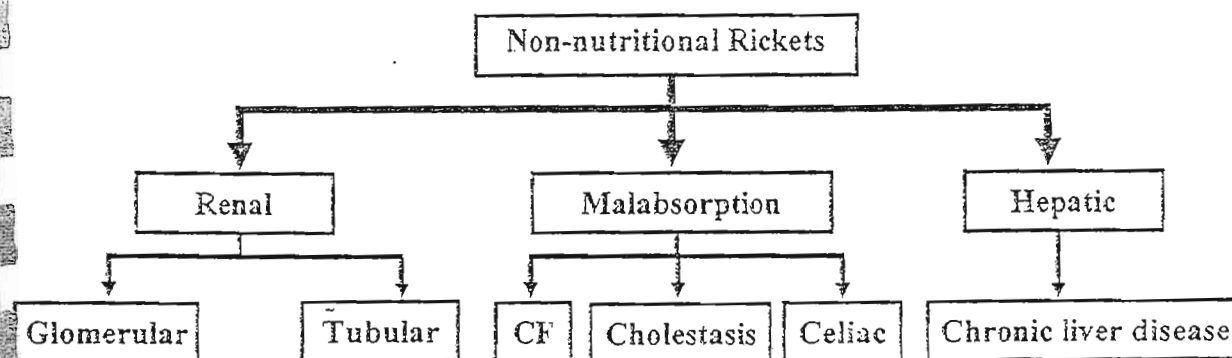
### B) Malabsorption

- Cystic fibrosis
- Celiac disease
- Chronic Cholestasis

### C) Hepatic rickets

- Chronic liver disease
- Due to defective vitamin D activation (25-hydroxylation) & defective bile secretion

## Remember



# Vitamin A Deficiency

## Clinical Picture

- Eye: Keratomalacia, xerophthalmia, blindness, bitot spots (= Conjunctival plaques)
- Skin: Dry, scaly skin
- Increased susceptibility to infections: GE & pneumonia

## Prevention

- Diet: Eggs, liver, fruits, vegetables
- Supplementation:
  - At the age of 12 months (with MMR vaccine): 100.000 IU
  - At the age of 18 months (with OPV, DPT & MMR vaccines): 200.000 IU

# Nutritional Requirements

## Balanced Diet should contain:

1. Adequate water
2. Adequate calories
  - CHO = 50 %
  - Lipids = 35 %
  - Proteins = 15 %
3. Adequate macronutrients [CHO, Lipids, Proteins]
4. Adequate micronutrients [Vitamins, minerals, trace elements]
5. Adequate amount of fibers "Fruits, vegetables, cereals" (Bulking effect, prevention of constipation)

## Energy, Water, Macronutrients

High biological value proteins	Low biological value proteins
Animal origin (milk, meat, eggs)	Vegetable origin (cereals, legumes)
Contain all essential amino acids	Not all essential amino acids

	Energy (Kcal/Kg/day)	Water (ml/Kg/day)	Proteins (gm/Kg/day)	Lipids	CHO
Infancy	100	120	2-2.5		
2-6 years	90	100	1.6-1.8		
6-12 years	70-80	80-90	1.2		
12-20 years	50-60	70-80	1		
Adults	40	40-50	0.8	1 gm/Kg/day	10 gm/Kg/day
Function	Energy is needed for: <ul style="list-style-type: none"> <li>- Basal metabolism (50%)</li> <li>- Physical activity (25%)</li> <li>- Growth (12%)</li> <li>- Fecal losses (8%)</li> <li>- Specific dynamic action of food (5%)</li> </ul>	Water constitutes: <ul style="list-style-type: none"> <li>▪ Infants: 75-80% of BW</li> <li>▪ Adults: 60 % of BW</li> </ul> <b>Remember</b> <ul style="list-style-type: none"> <li>- Breast milk = 87 % H<sub>2</sub>O</li> <li>- Infants are more liable to dehydration (see GE)</li> </ul>	Growth of tissues <ul style="list-style-type: none"> <li>- Cellular elements</li> <li>- Enzymes &amp; hormones</li> <li>- Blood proteins:               <ul style="list-style-type: none"> <li>▪ Hemoglobin</li> <li>▪ Coagulation factors</li> <li>▪ Oncotic pressure</li> <li>▪ Immunity (Ig)</li> <li>▪ Buffers</li> <li>▪ Viscosity</li> </ul> </li> </ul>	Energy (1 gm = 9 Kcal) <ul style="list-style-type: none"> <li>- Essential FA</li> <li>- Fat soluble vitamins</li> <li>- CNS development</li> <li>- Insulation</li> <li>- (Temperature control)</li> <li>- Support of viscera</li> <li>- Makes food palatable</li> </ul>	- Main source of energy
Related disorders	- Marasmus (↓↓ Calories) - Obesity (↑↑ Calories)	- Dehydration	- Kwashiorkor (Edema)		

## Vitamins & Minerals

Requirements	Vitamin A	Vitamin D	Vitamin C	Iron	Calcium
<b>Function</b>	2000 IU/day - Epithelial health ▪ Skin ▪ Mucous membrane (GIT & respiratory) - Retinal pigments ▪ Keratomalacia ▪ Xerophthalmia ▪ Corneal ulcers ▪ Blindness	400-800 IU/day - Normal bone mineralization - Ca, PO <sub>4</sub> metabolism	50 mg/day - BV integrity - Antioxidant - Iron absorption - Hemostasis	10-15 mg/day - Hb synthesis - Intracellular enzymes	500 mg/day - Normal bone mineralization - Nerve conduction - Hemostasis
<b>Related disorders</b>		▪ Rickets ▪ Osteomalacia	Scurvy	Iron deficiency anemia	Rickets

Requirements	Vitamin B1	Vitamin B2	Vitamin B6	Vitamin B12	Folic acid
<b>Function</b>	0.5-1 mg/day - Cofactors in metabolic pathways Skin integrity	0.5-1 mg/day - Cofactors in metabolic pathways	0.5-1 mg/day - Coenzyme - Hb synthesis	1-2 µg / day - CNS metabolism - Hb synthesis	200 µg / day - DNA synthesis
<b>Related disorders</b>	Beri-beri	▪ Cheilosis ▪ Glossitis ▪ Fissuring of mouth	▪ Neuropathy ▪ Convulsions ▪ Anemia	▪ Neuropathy ▪ Megaloblastic Anemia	Megaloblastic Anemia

## Mineral Metabolism

### Classification

Minerals are classified into 2 groups:

1. **Macrominerals** (= Principal elements): Calcium, Magnesium, Phosphorus, Sodium, Potassium, Chloride & Sulfur
2. **Microminerals** (= Trace elements): Iron, Copper, Manganese, Iodide, Fluoride, Cobalt, Molybdenum, Selenium & Chromium

	1. Macrominerals	2. Microminerals (Trace elements)
Body content	Grams / Kg body weight	Milligrams / Kg body weight
Daily requirement	> 100 mg	< 100 mg

## Vitamins

### Definition

- Organic nutrients required in minute amounts for normal growth & health
- They can not be synthesized in the body
- Not involved in tissue structure & not oxidized for energy production
- They are classified into 2 groups:

1. **Fat-soluble vitamins:** A, D, E, K
2. **Water-soluble vitamins:** B complex & vitamin C

## Micronutrients

Vitamins

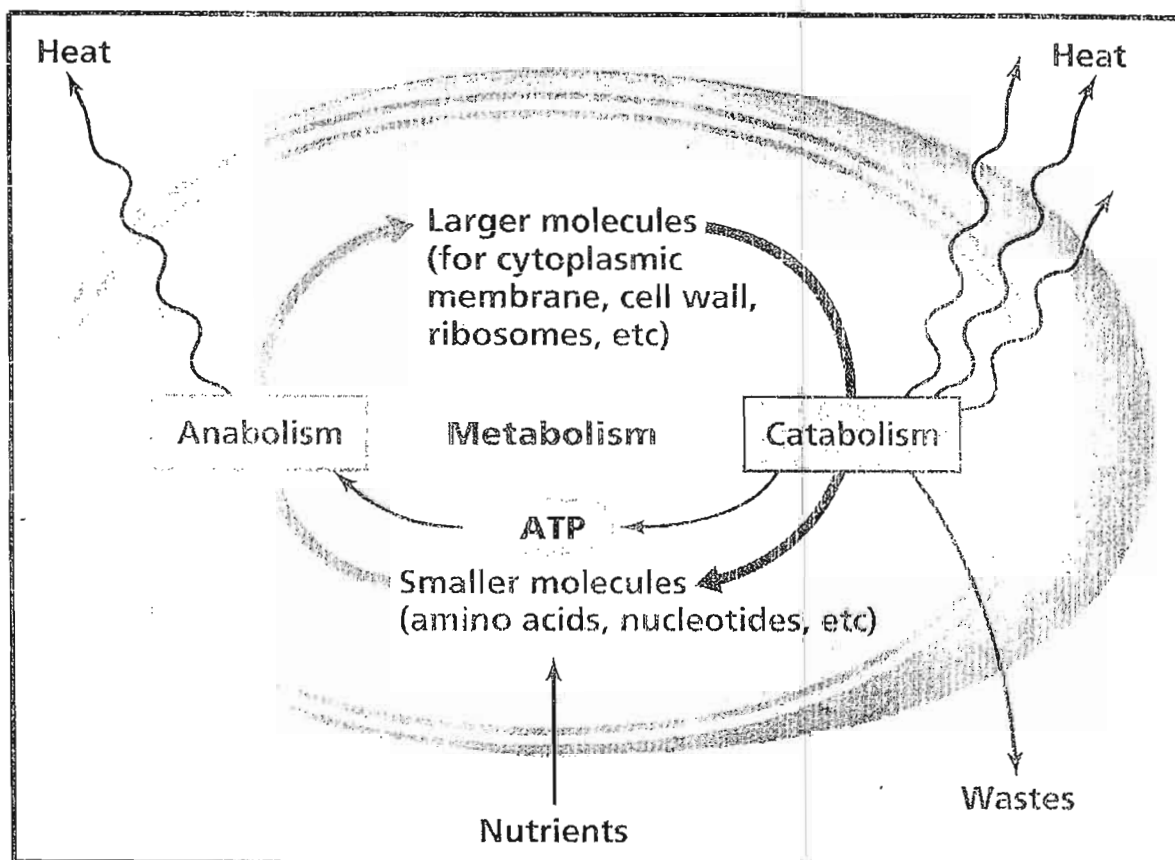
Trace elements

## Trace Elements

	Source	Physiology	Effects of deficiency	Effects of excess
<b>Iron</b>	<ul style="list-style-type: none"> <li>- Red meat</li> <li>- Organ meat</li> <li>- Egg yolk</li> <li>- Whole cereals</li> <li>- Vegetables</li> </ul>	<ul style="list-style-type: none"> <li>- Hemoglobin</li> <li>- Myoglobin</li> <li>- Cytochromes</li> <li>- Enzymes (MAO)</li> </ul>	See iron-deficiency anemia: Hematological, neurological, epithelial...	<b>A) Acute poisoning:</b> <ul style="list-style-type: none"> <li>- Nausea, vomiting</li> <li>- Diarrhea</li> <li>- Abdominal pain</li> <li>- Hypotension</li> <li>- Hypoglycemia</li> <li>- ↑↑ Liver enzymes</li> </ul> <b>B) Chronic excess</b> Chronic hemolytic anemia
<b>Copper</b>	<ul style="list-style-type: none"> <li>- Oysters</li> <li>- Nuts</li> <li>- Liver</li> </ul>	<ul style="list-style-type: none"> <li>- Essential component of:                         <ul style="list-style-type: none"> <li>➤ Superoxide dismutase</li> <li>➤ Cytochrome oxidase</li> <li>➤ Tyrosinase (<i>Melanin</i>)</li> </ul> </li> <li>- Iron absorption &amp; mobilization</li> <li>- Normal function of the CNS</li> </ul>	<ul style="list-style-type: none"> <li>- Microcytic anemia</li> <li>- Neurological symptoms</li> <li>- Depigmentation</li> <li>- Neutropenia</li> <li>- Osteoporosis</li> </ul>	<b>A) Acute poisoning:</b> <ul style="list-style-type: none"> <li>- Nausea, vomiting</li> <li>- Abdominal pain</li> <li>- ↑↑ Liver enzymes</li> </ul> <b>B) Chronic excess</b> Wilson disease
<b>Fluoride</b>	<ul style="list-style-type: none"> <li>- Toothpaste</li> <li>- Fluorinated water</li> </ul>	<ul style="list-style-type: none"> <li>- Essential component of:                         <ul style="list-style-type: none"> <li>➤ Bone</li> <li>➤ Teeth</li> </ul> </li> <li>- Formation of thyroid hormones</li> </ul>	<ul style="list-style-type: none"> <li>- Dental caries</li> </ul>	<ul style="list-style-type: none"> <li>- Fluorosis: Brittle teeth</li> <li>- Teeth mottling</li> </ul>
<b>Iodine</b>	<ul style="list-style-type: none"> <li>- Iodized table salt</li> <li>- Near sea</li> <li>- Saltwater fish</li> </ul>	<ul style="list-style-type: none"> <li>- Formation of thyroid hormones</li> </ul>	<ul style="list-style-type: none"> <li>- Hypothyroidism</li> </ul>	<ul style="list-style-type: none"> <li>- Hypothyroidism, goiter</li> <li>- Maternal Iodine excess: congenital hypothyroidism</li> </ul>
<b>Manganese</b>	<ul style="list-style-type: none"> <li>- Nuts</li> <li>- Tea</li> </ul>	<ul style="list-style-type: none"> <li>- Essential component of:                         <ul style="list-style-type: none"> <li>➤ Superoxide dismutase</li> <li>➤ Arginase, choline esterase</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Hypercholesterolemia</li> </ul>	<ul style="list-style-type: none"> <li>- Neurological symptoms</li> <li>- Cholestasis</li> </ul>

<b>Selenium</b>	<ul style="list-style-type: none"> <li>- Seafood</li> <li>- Meat</li> <li>- Garlic</li> </ul>	<ul style="list-style-type: none"> <li>- Enzyme cofactor of: <ul style="list-style-type: none"> <li>➤ Glutathione peroxidase</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Cardiomyopathy</li> <li>- Myopathy</li> </ul>	<ul style="list-style-type: none"> <li>- Neurological symptoms</li> <li>- Nausea, diarrhea</li> <li>- Garlic odor</li> </ul>
<b>Zinc</b>	<ul style="list-style-type: none"> <li>- Shellfish</li> <li>- Meat</li> <li>- Cheese</li> </ul>	<ul style="list-style-type: none"> <li>- Essential component of: <ul style="list-style-type: none"> <li>➤ Superoxide dismutase</li> <li>➤ Carbonic anhydrase</li> </ul> </li> <li>- Insulin storage</li> </ul>	<ul style="list-style-type: none"> <li>- Circumoral &amp; perianal rash</li> <li>- Poor wound healing</li> <li>- Alopecia, chronic diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>- Nausea, vomiting</li> <li>- Diarrhea</li> <li>- Abdominal pain</li> </ul>
<b>Chromium</b>	<ul style="list-style-type: none"> <li>- Brewer's Yeast</li> <li>- Meat</li> </ul>	<ul style="list-style-type: none"> <li>- Potentiates insulin action</li> </ul>	<ul style="list-style-type: none"> <li>- Impaired glucose tolerance</li> <li>- Peripheral neuropathy</li> <li>- Encephalopathy</li> </ul>	<ul style="list-style-type: none"> <li>- Unknown?</li> </ul>
<b>Molybdenum</b>	<ul style="list-style-type: none"> <li>- Brewer's Yeast</li> <li>- Meat</li> </ul>	<ul style="list-style-type: none"> <li>- Essential component of: <ul style="list-style-type: none"> <li>➤ Xanthine oxidase</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Impaired glucose tolerance</li> <li>- Peripheral neuropathy</li> <li>- Encephalopathy</li> </ul>	<ul style="list-style-type: none"> <li>- Unknown?</li> </ul>





# Inborn Errors of Metabolism

*(For Master degree)*

By

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**Assistant Professor of Pediatrics**

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**2013**

# Inborn Errors of Metabolism

## Definition

- Group of inherited biochemical disorders caused by enzyme, coenzyme, receptor, membrane or transport defect

## Presentation

- Variable severity [Mild-Severe-Lethal]
- Variable age of onset

## Biochemical Defect

### A) Enzyme Defects

**Enzymes:** Biological catalysts. Virtually all enzymes are proteins (either simple or conjugated). Conjugated enzyme (holoenzyme) = Apoenzyme + Coenzyme

**Apoenzyme:** It is the protein part of the holoenzyme

**Coenzyme:** It is the organic non-protein part of the holoenzyme (e.g., vitamin...)

**Enzyme defect** leads to metabolic block:

- Accumulation of precursors

Disease	Enzyme Defect	Accumulated substance
Galactosemia	Galactose 1-P-uridyltransferase	Galactose & Galactitol
GSD (Von Gierke)	Glucose 6-Phosphatase	Glycogen
Gaucher	Glucocerebrosidase ( $\beta$ -Glucosidase)	Glucocerebrosides (glycolipid)
Niemann-Pick	Sphingomyelinase	Sphingomyeline
MPS (Hurler)	$\alpha$ -L- Iduronidase	GAG = Glycosaminoglycan
GM <sub>1</sub> Gangliosidosis	$\beta$ -Galactosidase	Gangliosides
GM <sub>2</sub>	Tay-Sachs	Hexosaminidase A
	Sandhoff	Hexosaminidase A & B

- Deficiency of end-product

Albinism: ( $\downarrow\downarrow$  Melanin) Tyrosine  $\xrightarrow{\text{Tyrosinase}}$  Melanin

- Opening of alternative pathway

Normally: Phenylalanine  $\xrightarrow{P.\text{hydroxylase}}$  Tyrosine  
 Phenylketonuria:  $\uparrow\uparrow$  Phenylalanine  $\rightarrow$   $\uparrow\uparrow$  Phenylpyruvate, lactate & acetate

### B) Transport across cell membranes

- Transport across cell membrane

Specific vitamin B<sub>12</sub> malabsorption due defective receptors for IF-B<sub>12</sub> complex

- Transport across lysosomal membrane

Cystinosis: Trapping of cystine inside the lysosomes. [Action of Cysteamine??]

### C) Binding Proteins

- Hemoglobin carries O<sub>2</sub>: HbM cannot carry O<sub>2</sub>
- Ceruloplasmin carries Copper: Wilson disease

## When to suspect (= Clinical Picture)

1. **Neonatal Presentation:** Poor feeding, lethargy, vomiting, seizures [DD: Sepsis, ↓↓Ca, ↓↓G]
2. **Consanguineous parents & positive family history**
3. **Unexplained MR, coma, convulsions or developmental delay**
4. **Unexplained vomiting, acidosis**
5. **Unexplained organomegaly (Hepatomegaly)**
6. **Unexplained odor:**
  - ☒ **PKU:** Mousy or musty
  - ☒ **Tyrosinemia (& Hypermethioninemia):** Boiled cabbage
  - ☒ **Maple syrup urine:** Maple syrup
  - ☒ **Isovaleric acidemia:** Sweaty foot
  - ☒ **Multiple carboxylase deficiency:** Tomcat urine
7. **Unexplained muscle weakness or cardiomyopathy**
8. **Unexplained renal stones**
9. **Episodic pattern (with disease-free intervals)**



## Neonatal screening (American College of Medical Genetics = ACMG)

	Primary Disorders	Secondary Disorders
<b>Organic acid</b>	<ul style="list-style-type: none"> <li>▣ Methylmalonic acidemia</li> <li>▣ Propionic acidemia</li> <li>▣ Isovaleric acidemia</li> <li>▣ Glutaric aciduria type I</li> <li>▣ Multiple carboxylase deficiency</li> <li>▣ Beta-ketothiolase deficiency</li> </ul>	<ul style="list-style-type: none"> <li>▣ Malonic acidemia</li> </ul>
<b>Fatty acids</b>	<ul style="list-style-type: none"> <li>▣ MCAD, VLCAD, LCHAD</li> <li>▣ Carnitine uptake defect</li> </ul>	<ul style="list-style-type: none"> <li>▣ Carnitine palmitoyl transferase I deficiency</li> <li>▣ Carnitine palmitoyl transferase II deficiency</li> </ul>
<b>Amino acids</b>	<ul style="list-style-type: none"> <li>▣ Phenylketonuria</li> <li>▣ Maple syrup urine disease</li> <li>▣ Homocystinuria</li> <li>▣ Citrullinemia</li> <li>▣ Argininosuccinic acidemia</li> <li>▣ Tyrosinemia (type I)</li> </ul>	<ul style="list-style-type: none"> <li>▣ Tyrosinemia type II</li> <li>▣ Tyrosinemia type III</li> </ul>
<b>Hemoglobin</b>	<ul style="list-style-type: none"> <li>▣ Sickle cell anemia</li> <li>▣ Hemoglobin S-β-thalassemia</li> <li>▣ Hemoglobin SC disease</li> </ul>	<ul style="list-style-type: none"> <li>▣ Hemoglobin variant (Hemoglobin E)</li> </ul>
<b>Others</b>	<ul style="list-style-type: none"> <li>▣ Congenital hypothyroidism</li> <li>▣ Biotinidase deficiency</li> <li>▣ Congenital adrenal hyperplasia</li> <li>▣ Galactosemia</li> <li>▣ Hearing deficiency</li> <li>▣ Cystic fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>▣ Galactose epimerase deficiency</li> <li>▣ Galactokinase deficiency</li> </ul>

# Treatment of Genetic Diseases

## 1. Enzyme Induction

Phenobarbitone in Crigler-Najjar syndrome type II (AD)

## 2. Enzyme Replacement

- ☒ Gaucher disease
- ☒ Pompe disease (GSD type II)
- ☒ Fabry disease
- ☒ ADA deficiency
- ☒ Some MPS
- ☒ Cystic fibrosis

## 3. Recombinant proteins

- ☒ GH
- ☒ Insulin
- ☒ Factor VIII
- ☒ EPO
- ☒ GM-CSF
- ☒ Interferon

## 4. Replacement of Hormones

- ☒ Hydrocortisone (CAH)
- ☒ 9- $\alpha$  fludrocortisol (CAH)
- ☒ GH (Hypopituitarism)
- ☒ Thyroxine (Congenital hypothyroidism)

## 5. Replacement of vitamins

- ☒ B<sub>1</sub> (Maple syrup urine disease)
- ☒ B<sub>6</sub> (Homocystinuria)
- ☒ B<sub>12</sub> (Methylmalonic acidemia)
- ☒ Biotin (Propionic acidemia)
- ☒ Folic acid (Megaloblastic anemia)
- ☒ Vitamin D (Vitamin D resistant rickets)

## 6. Dietary restriction

- ☒ Maple syrup urine (V I L)
- ☒ Methionine (Homocystinuria)
- ☒ PKU (Phenylalanine)
- ☒ Urea cycle disease (proteins)
- ☒ Galactosemia (galactose, Lactose)
- ☒ Hypercholesterolemia (Lipids)

## 7. Induction of alternative pathways

Na benzoate in urea cycle defects (to eliminate NH<sub>3</sub>)

## 8. Preventive therapy

Avoidance of certain drugs in G6PD deficiency

## 9. BM or liver transplantation

## 10. Portocaval anastomosis

In cases of portal hypertension (GSD type IV)

## 11. Extracorporeal therapy

Plasmapheresis in the Rx of hypercholesterolemia

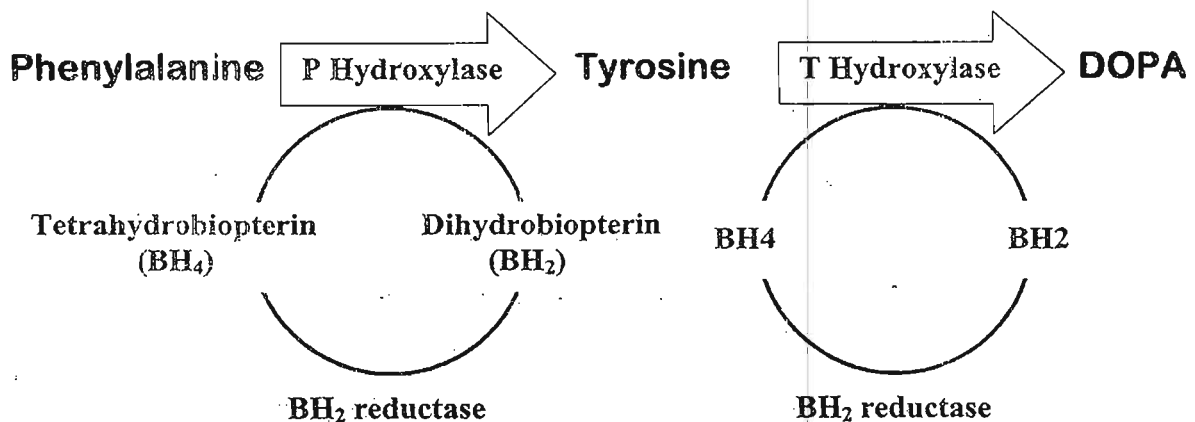
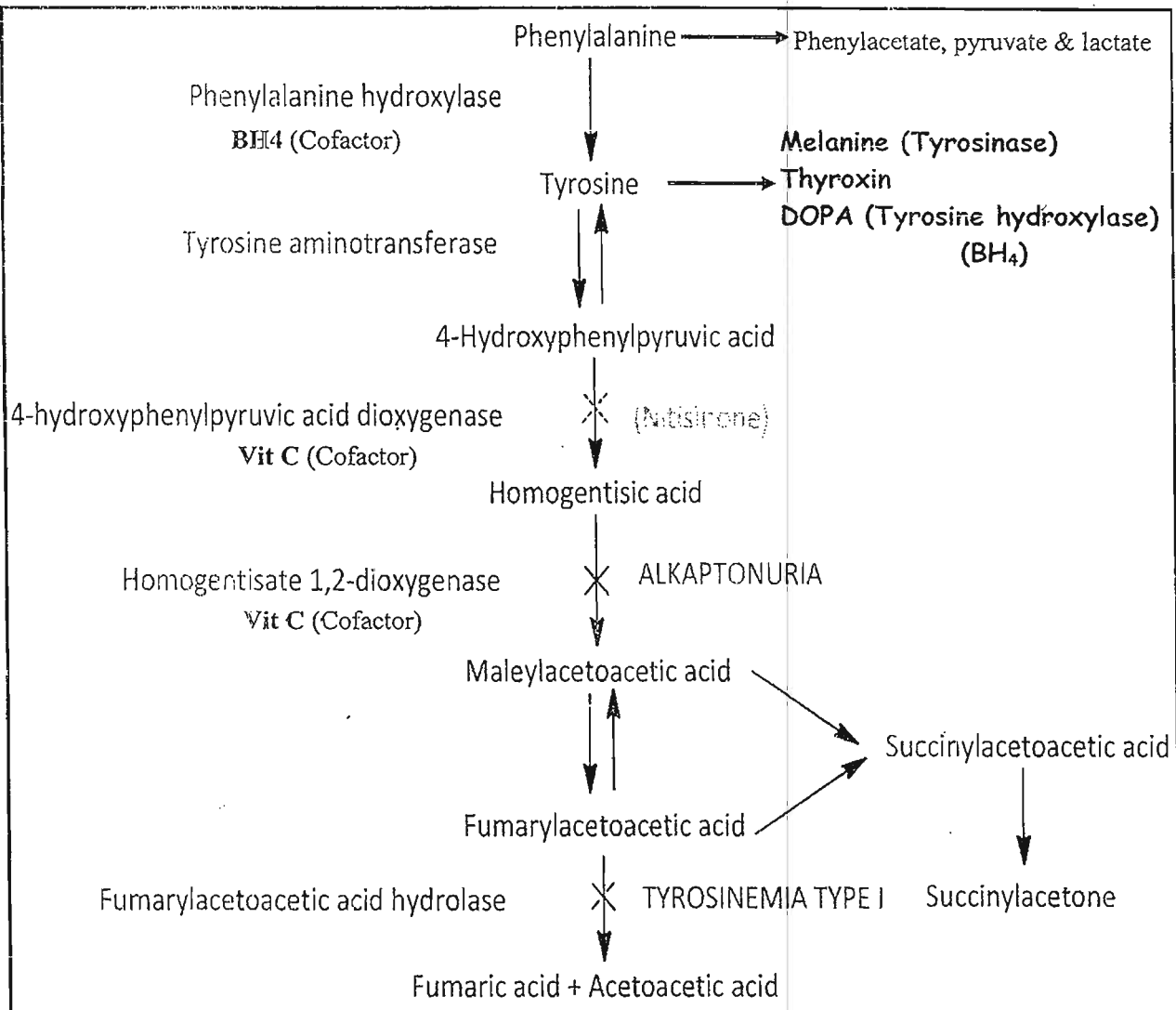
## 12. Gene therapy (Give examples)

### Note

Essential Amino acids	Non-essential Amino acids
<ul style="list-style-type: none"> <li>▪ Phenylalanine</li> <li>▪ Valine, leucine, isoleucine</li> <li>▪ Threonine, methionine</li> <li>▪ Arginine, lysine, histidine</li> <li>▪ Tryptophan</li> </ul>	<ul style="list-style-type: none"> <li>▪ Tyrosine</li> <li>▪ Glycine glutamic, glutamine</li> <li>▪ Alanine, proline</li> <li>▪ Cysteine, serine</li> <li>▪ Aspartic, asparagine</li> </ul>

# Disorders of Protein Metabolism

## Phenylalanine & Tyrosine



# Phenylketonuria

## Definition

- AR (12q for PAH)
- **Classic PKU:** Plasma phenylalanine level > 20 mg/dL
- **Non-PKU hyperphenylalaninemia:** Plasma phenylalanine level < 20 mg/dL [but > 2 mg/dL]

## Biochemical Defect

- $\downarrow\downarrow$  Phenylalanine hydroxylase  $\rightarrow$   $\uparrow\uparrow$  Phenylalanine  $\rightarrow$  CNS damage (mechanism?)

## Epidemiology

- **Non-PKU hyperphenylalaninemia:** 1:50.000 live births
- More common in whites

## Clinical Picture (Classic PKU)

- Normal at birth
- CNS: Seizures (25%), spasticity, tremors, microcephaly, MR "Normal mentality in 2-5%"
- Skin: Light complexion (*Blond, blue eyes*), seborrheic rash, eczema
- Vomiting

## Investigations

- Neonatal screening
  - Past: Bacterial inhibition test of Guthrie
  - Now: TMS
  - Time: In the 1<sup>st</sup> 48 hrs after protein intake is recommended
- Plasma phenylalanine
- EEG: Abnormalities in > 50%
- MRI & MRS:  $\uparrow\uparrow$  Phenylalanine
- Prenatal diagnosis is available (CVS)

## Treatment

- Phenylalanine restricted diet for **life**
  - Target level: 2-6 mg/dL
  - Phenylalanine deficiency: Lethargy, FTT, anemia, anorexia, diarrhea
  - Tyrosine becomes essential
- Oral BH<sub>4</sub> (10 mg/Kg/day):  $\downarrow\downarrow$  Phenylalanine level in 50% of cases

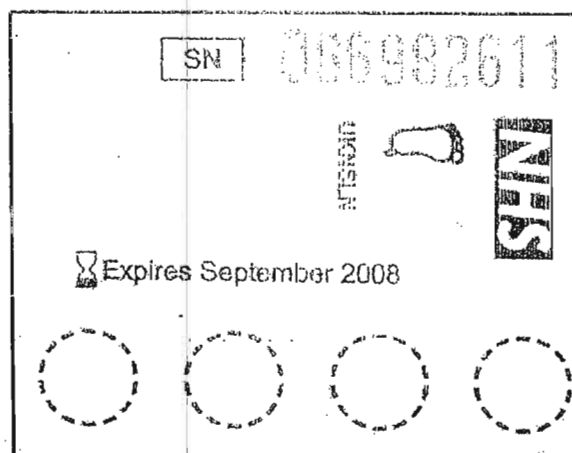


## Maternal PKU

**Mechanism:** Phenylalanine is teratogenic

**C/P:** Microcephaly, MR, CHD

**Prevention:** Phenylalanine-restricted diet  
(Phe level should be < 6 mg/dL)



# **Hyperphenylalaninemia due to BH4 deficiency**

## **Biochemical Defect**

- BH4 is a cofactor for PAH, Tyrosine hydroxylase, Tryptophan hydroxylase & NO synthase
- So, important in synthesis of dopamine & serotonin [Neurotransmitters]

## **Epidemiology**

- 1-3% of infants with hyperphenylalaninemia are due to defect in BH4 metabolism

## **Clinical Picture**

- Extrapyrimalidal: Choreoathetosis, dytonia, hypotonia (Diurnal variation)
- Seizures, MR
- Hyperprolactinemia (why?)

## **Investigations**

- Neonatal screening & plasma phenylalanine: Hyperphenylalaninemia
- BH4 loading test: ↓↓ plasma phenylalanine level
- ↓↓ CSF dopamine & serotonin
- Urinary biopterin
- Enzyme assay?? (Blood & liver)

## **Treatment**

- Phenylalanine restricted diet
- Oral BH4
- Neurotransmitters precursors: Dopa & tryptophan [Carbidopa should be given, why?]

## **BH4 deficiency without Hyperphenylalaninemia (= AD Dopa-responsive dystonia = Segawa syndrome)**

**Biochemical Defect** ↓↓ BH4 occurs due to GTP cyclohydrolase deficiency (AD form)

**Clinical Picture** Extrapyrimalidal: Dytonia starting in the LL (Diurnal variation)

## **Investigations**

- No Hyperphenylalaninemia,
- ↓↓ CSF dopamine
- Enzyme assay & gene analysis

**Treatment** Dopa [Carbidopa should be given]

# Tyrosinemia type I

## Definition

- AR
- Severe disease affecting liver, kidney & peripheral nerves

## Biochemical Defect

- $\downarrow\downarrow$  Fumarylacetoacetate hydrolase  $\rightarrow$   $\uparrow\uparrow$  Succinylacetone  $\rightarrow$  Organ damage

## Epidemiology

- 1:1000.000 live births (More common in those with French & Scandinavian ancestry)

## Clinical Picture (Onset = 2-6 months of age)

### A. Hepatic affection

- Fever, irritability, vomiting, hepatomegaly, jaundice, hypoglycemia, coagulopathy
- Boiled cabbage odor ( $\uparrow\uparrow$  Methionine, why?)
- Liver cell failure, cirrhosis, hepatocellular carcinoma (> 2 yrs)

### B. Renal affection

- Proximal RTA
- Vitamin D-resistant rickets

### C. Peripheral neuropathy

- Pain, hypertonia, paralysis

## Investigations

- $\uparrow\uparrow$  Blood & urine succinylacetone
- $\uparrow\uparrow$   $\alpha$ -Fetoprotein (**Marked**)
- Investigation of liver, hematologic & renal affection: ALT, AST, bilirubin, glucose, CBC
- Plasma tyrosine level??
- Neonatal screening (succinylacetone)
- Prenatal diagnosis is available (AF succinylacetone or CVS)

## Treatment

- Phenylalanine & tyrosine restricted diet
- Nitisinone (NTBC):
  - Originally developed as a herbicide
  - Mechanism:
    - 2-Nitro-4-trifluoromethylbenzoyl-1,3-cyclohexanedione
    - Tyrosine corneal crystals may develop
- Liver transplantation



	<b>Tyrosinemia II (Oculocutaneous)</b>	<b>Tyrosinemia III</b>
<b>Defect</b>	$\downarrow\downarrow$ Tyrosine aminotransferase	$\downarrow\downarrow$ Hydroxyphenylpyruvate dioxygenase
<b>Genetics</b>	AR (16q)	AR (12q)
<b>C/P</b>	<ul style="list-style-type: none"> <li>▪ <b>Skin:</b> Palmar &amp; plantar keratosis</li> <li>▪ <b>Ocular:</b> Pain, redness, <math>\uparrow\uparrow</math> tears, ulcer</li> <li>▪ <b>MR:</b> Mild</li> </ul>	<ul style="list-style-type: none"> <li>▪ Seizures, MR, ataxia</li> <li>▪ Self mutilation</li> </ul>
<b>Diagnosis</b>	▪ $\uparrow\uparrow$ Plasma tyrosine	<ul style="list-style-type: none"> <li>▪ <math>\uparrow\uparrow</math> Plasma tyrosine</li> <li>▪ <math>\uparrow\uparrow</math> urine HPP</li> </ul>
<b>TTT</b>	▪ Phenylalanine & tyrosine restricted diet	▪ Diet + Vitamin C



# **Alkaptonuria**

## **Definition**

- AR (3q), rare (1:250.000)

## **Biochemical Defect**

- ↓↓ Homogentisic acid dioxygenase → ↑↑ Homogentisic acid → Tissue accumulation

## **Clinical Picture**

- The only sign of alcaptonuria in children is "black urine on standing"
- Ochronosis: Darkening of tissues (sclera & ear)
- Arthritis (big joints): Adult

## **Investigations**

- ↑↑ Urine homogentisic acid

## **Treatment**

- Phenylalanine & tyrosine restricted diet
- Nitisinone (NTBC)
- Vitamin C

# **Transient Tyrosinemia of the Newborn**

## **Definition**

- ↑↑ Tyrosine level in premature neonates (receiving ↑↑ protein diet)

## **Biochemical Defect** Immature HPPD → ↑↑ Tyrosine level

## **Clinical Picture** Lethargy, poor feeding, screening tests

## **Investigations** ↑↑ Plasma tyrosine & ↑↑ urine hydroxyphenylpyruvic acid

## **Treatment** Dietary protein restriction & Vitamin C

# **Tyrosine Hydroxylase Deficiency**

(= AR Dopa-responsive dystonia = Infantile Parkinsonism)

## **Definition**

- AR disease due to DOPA deficiency

## **Biochemical Defect**

- Tyrosine hydroxylase deficiency
- Tyrosine → DOPA

## **Clinical Picture** (as Segawa syndrome)

- Extrapyramidal: Dystonia, hypertonia, oculogyric crises, infantile parkinsonism
- No diurnal variation

## **Investigations**

- ↓↓ CSF dopamine

## **Treatment**

- Dopa [Carbidopa should be given]

# Albinism

## Definitions

- **Albinism:** Complete or partial absence of melanin pigment in the skin, hair & eyes
- **Melanocyte:** are melanin-producing cells located in skin (epidermis), eye & inner ear
- **Melanosome:** Organelle containing melanin
- **Melanin:** is a dark pigment present in skin, eye & hair (absorb UV rays)
- **Optical system development** is highly dependent on the presence of melanin

## Biochemical Defect

- Tyrosine  $\longrightarrow$  Melanin
- Types of melanin: **Pheomelanin** (yellow-red) & **Eumelanin** (Brown-black)
- Albinism may be Oculocutaneous (generalized), ocular or localized
- Albinism may be complete (No pigment at all) or partial

## Clinical Picture

### A. Skin affection

- Lack of skin pigment (Fair or white skin)
- $\uparrow\uparrow$  Risk of sunburn & skin cancers

### B. Visual affection

- Photophobia,  $\downarrow\downarrow$  visual acuity, red reflex
- Nystagmus, squint, astigmatism, amblyopia "Poor transmission to the brain"
- Optic nerve hypoplasia, foveal hypoplasia
- Abnormal decussation of optic nerve fibres (abnormal VEP)

### C. Ear affection

- $\uparrow\uparrow$  Susceptibility to ototoxic drugs

Treatment Avoid sun exposure & use of sunscreens (with high SPF)

## Oculocutaneous Albinism

	Defect	Manifestations	
<b>OCA1</b>	Tyrosinase deficiency	<b>OCA1A</b> (Severe)	<ul style="list-style-type: none"> <li>▪ Evident at birth &amp; persistent (remains unchanged)</li> <li>▪ Milky white skin, white hair, red gray eyes</li> <li>▪ No tan, No pigmented nevi</li> </ul>
		<b>OCA1B</b> (Mild)	<ul style="list-style-type: none"> <li>▪ Evident at birth &amp; improve with age</li> <li>▪ Light blond skin &amp; light blue eyes</li> <li>▪ Can develop pigmented nevi &amp; tan</li> </ul>
<b>OCA2</b>	Normal Tyrosinase	<ul style="list-style-type: none"> <li>▪ At birth: Some pigmentation &amp; <math>\uparrow\uparrow</math> with age (pigment accumulation)</li> <li>▪ Yellow hair, red gray eyes</li> <li>▪ Can develop pigmented nevi (Not tan)</li> <li>▪ <b>Prader-Willi &amp; Angelman</b> may have some <math>\downarrow\downarrow</math> pigments</li> </ul>	
<b>OCA3</b>		<ul style="list-style-type: none"> <li>▪ Reddish hair</li> <li>▪ Reddish brown skin</li> </ul>	
<b>OCA4</b>		<ul style="list-style-type: none"> <li>▪ Similar to OCA2</li> </ul>	
<b>Hermansky-Pudlak</b>		<ul style="list-style-type: none"> <li>▪ AR (Defect in melanosomes &amp; platelet dense bodies)</li> <li>▪ OCA, platelet dysfunction (why?)</li> </ul>	
<b>Chediak-Higashi</b>		<ul style="list-style-type: none"> <li>▪ Immunodeficiency, silvery hair, light skin</li> <li>▪ Defective degranulation (Neutropenia, platelet dysfunction)</li> </ul>	

## Ocular Albinism

- XLR
- Visual manifestation with **normal** skin pigmentation
- Late-onset sensorineural deafness has been reported

## Localized Albinism

### A. Piebaldism

- AD condition
- White forelock
- White macules on the face, trunk & extremities

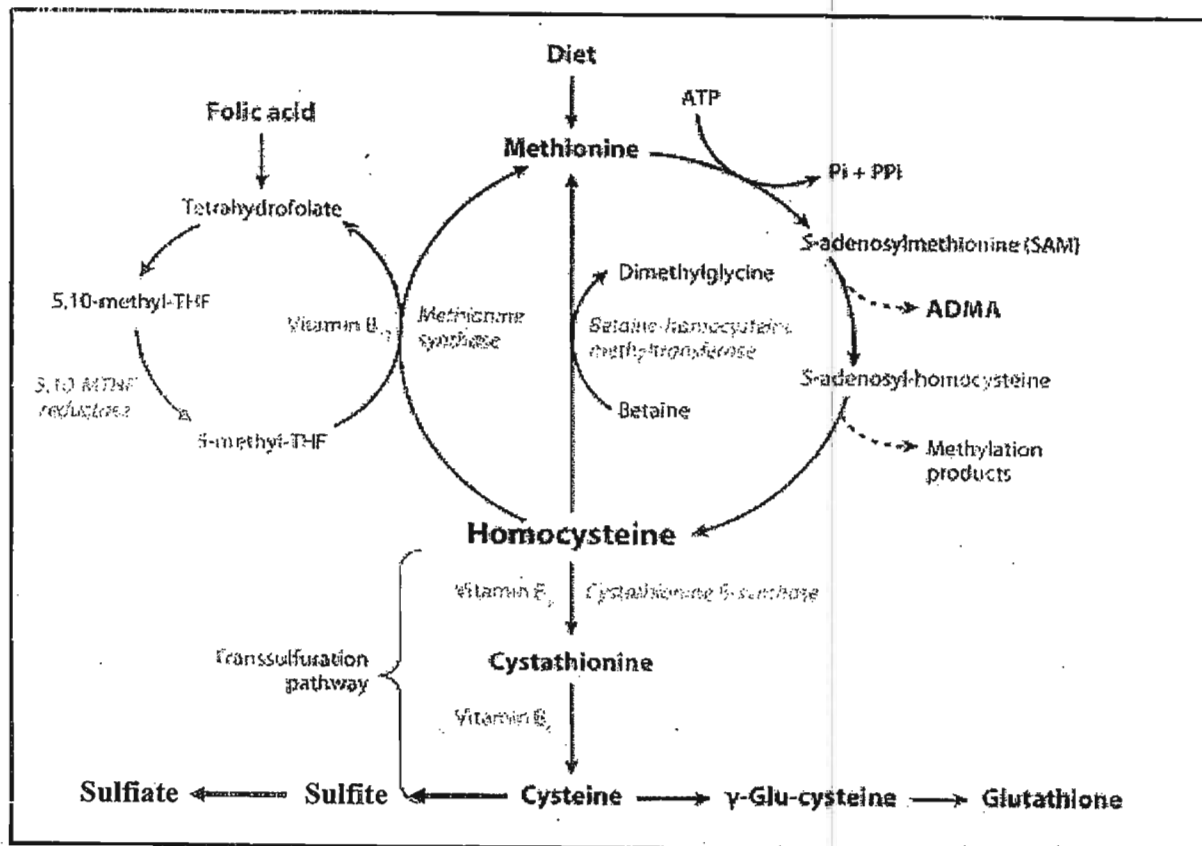
### B. Waardenburg syndrome

- AD condition (2q, 3p), 4 types
- White forelock
- Broad nasal bridge, heterochromia, sensorineural deafness,

### C. Hypomelanosis of Ito

- Hypopigmentation following Blaschko's lines (*Invisible skin lines*)

## Methionine Metabolism



### Biochemical Defect

- Methionine is an essential amino acid
- Methionine catabolism: Methyl group donor & cysteine
- Most homocysteine is remethylated to methionine (catalyzed by methionine synthase)

## Homocystinuria

	<b>Homocystinuria</b>	<b>Marfan syndrome</b>
<b>Etiology</b>	Cystathionine synthase ↓↓	Defect in collagen fibers
<b>Inheritance</b>	AR	AD
<b>Mentality</b>	MR	Normal
<b>Muculoskeletal</b>	Arachnodactyly (2 Tests), Pectus excavatum, High arched palate, Kyphoscoliosis	The same + Hernias Pneumothorax
<b>Bone density</b>	Osteoporosis	Normal
<b>Joints</b>	Stiff	Lax
<b>Cardiovascular</b>	AR, MR	AR, MR, Aortic dissection
<b>Ocular</b>	Myopia Lens dislocation (Downwards)	Myopia Lens dislocation (Upwards)
<b>Vascular thrombosis</b>	↑↑ risk of thrombosis	No ↑↑ risk of thrombosis
<b>Investigations</b>	↑↑ Homocystine in urine	No ↑↑ Homocystine in urine
<b>Treatment</b>	Low methionine diet B6 & folic acid	Supportive

## Cysteine & Cystine Metabolism

### Cystinuria & Cystinosis

## Tryptophan

### Hartnup Disease

#### Definition

- AR (5p), 1: 30.000
- Named after the 1<sup>st</sup> affected reported family

#### Biochemical Defect

- Defective intestinal & renal transport of neutral amino acids
- ↓↓ Intestinal absorption of tryptophan → ↑↑ Indole derivatives → Blue diaper syndrome
- ↑↑ Renal excretion of tryptophan
- Tryptophan is essential for niacin synthesis → Niacin deficiency

#### Clinical Picture (Pellagra-like)

- Skin: Cutaneous photosensitivity, rash, eczema
- CNS: Ataxia (intermittent), depression
- GIT: Glossitis

#### Investigations

- Neonatal screening
- ↑↑ Urine **neutral** amino acids (Tryptophan, phenylalanine, tyrosine, alanine...)

#### Treatment Nicotinic acid

DD: Fanconi syndrome

# Urea Cycle & Hyperammonemia

## Definition

- The function of urea cycle is to get rid of ammonia (Free  $\text{NH}_3$  is highly toxic)

## Biochemical Defect Co AAAN

- Five enzymes are involved in synthesis of urea:

- Carbamyl phosphate synthetase (CPS)
- Ornithine transcarbamylase (OTC)\*
- Argininosuccinate synthetase (AS): Citrullinemia
- Argininosuccinate lyase (AL): Argininosuccinic aciduria
- Arginase: Hyperargininemia
- N-acetylglutamate synthetase (activator of CPS)



All are AR except  
OTC

## Epidemiology

- 1:30.000 live births
- Most common genetic cause of hyperammonemia

## Clinical Picture

### A. Neonatal period

- Normal at birth
- Poor feeding, vomiting, tachypnea
- Lethargy, coma, convulsions,  $\uparrow\uparrow$  ICT
- Hepatomegaly

**Plasma  $\text{NH}_3$  should be done in any ill infant without evidence of infection**

### B. Infants & older children

- Vomiting
- CNS: Ataxia, confusion, irritability (alternating with lethargy & coma)

## Investigations

- $\uparrow\uparrow$   $\text{NH}_3$  [Normal values: < 35 (children), < 100 (FT), < 150  $\mu\text{mol/L}$  (Preterm)]
- $\downarrow\downarrow$  BUN,  $\uparrow\uparrow$  ALT, AST
- ABG: Respiratory alkalosis, why?
- Metabolites
  - CPS, OTC & NAG deficiency:  $\uparrow\uparrow$  Glutamine & alanine and  $\downarrow\downarrow$  arginine & citrulline
  - OTC deficiency:  $\uparrow\uparrow$  urinary orotic acid
  - Oral carbamylglutamate improve patients with NAG synthetase (Not CPS)
  - AS, AL, arginase deficiency:  $\uparrow\uparrow$  citrulline,  $\uparrow\uparrow$  argininosuccinic acid,  $\uparrow\uparrow$  arginine

## **Inborn Errors of Metabolism causing Hyperammonemia:**

- Urea cycle defects: 6 enzymes Co AAAN
- Organic acidemia MPI MBHG
  - Methylmalonic acidemia
  - Propionic acidemia
  - Isovaleric acidemia
  - Multiple carboxylase deficiency
  - Beta-ketothiolase deficiency
  - 3-(OH)-3-methylglutaric aciduria
  - Glutaric aciduria type II
- Lysinuric protein intolerance
- Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome HHH synd
- Transient hyperammonemia of the newborn THAN
- Congenital hyperinsulinism with hyperammonemia

## Treatment of Acute Hyperammonemia

### 1. Adequate Calories:

- IV fluid: electrolytes
- Glucose 10%
- Lipids: 1-2 g/Kg/day

**TTT of hyperammonemia should be rapid & aggressive (NH<sub>3</sub> is toxic)**

### 2. Protein restriction

- Protein: 0.25 g/Kg/day
- Essential amino acids are preferred

### 3. Enhancement of ammonia excretion

- Priming dose (250 mg/Kg to be added to 20 mL/Kg G10% over 1-2 hrs) of:
  - Na benzoate: Removes NH<sub>3</sub> in the form of hippuric acid
  - Phenylacetate: Removes NH<sub>3</sub> in the form of phenylacetylglutamine
  - Arginine: Except in arginase deficiency
- Maintenance infusion (250 mg/Kg/day): Na benzoate, phenylacetate or arginine

### 4. Dialysis

- If there is no significant decrease of NH<sub>3</sub>
- Hemodialysis is preferred

### 5. Oral neomycin

- ↓↓ Intestinal production of NH<sub>3</sub>

### 6. Oral lactulose

- ↓↓ Intestinal absorption of NH<sub>3</sub>

## Long-Term Treatment of Hyperammonemia

### 1. Adequate Calories

### 2. Protein restriction

- Protein: 1-2 g/Kg/day

### 3. Enhancement of ammonia excretion

- Na benzoate
- Phenylacetate
- Arginine
- Citrulline: In OTC deficiency

### 4. Carnitine supplementation

### 5. Avoid triggering factors: Infections, fasting

### 6. Avoid valproate, why?

## Transient Hyperammonemia of the newborn:

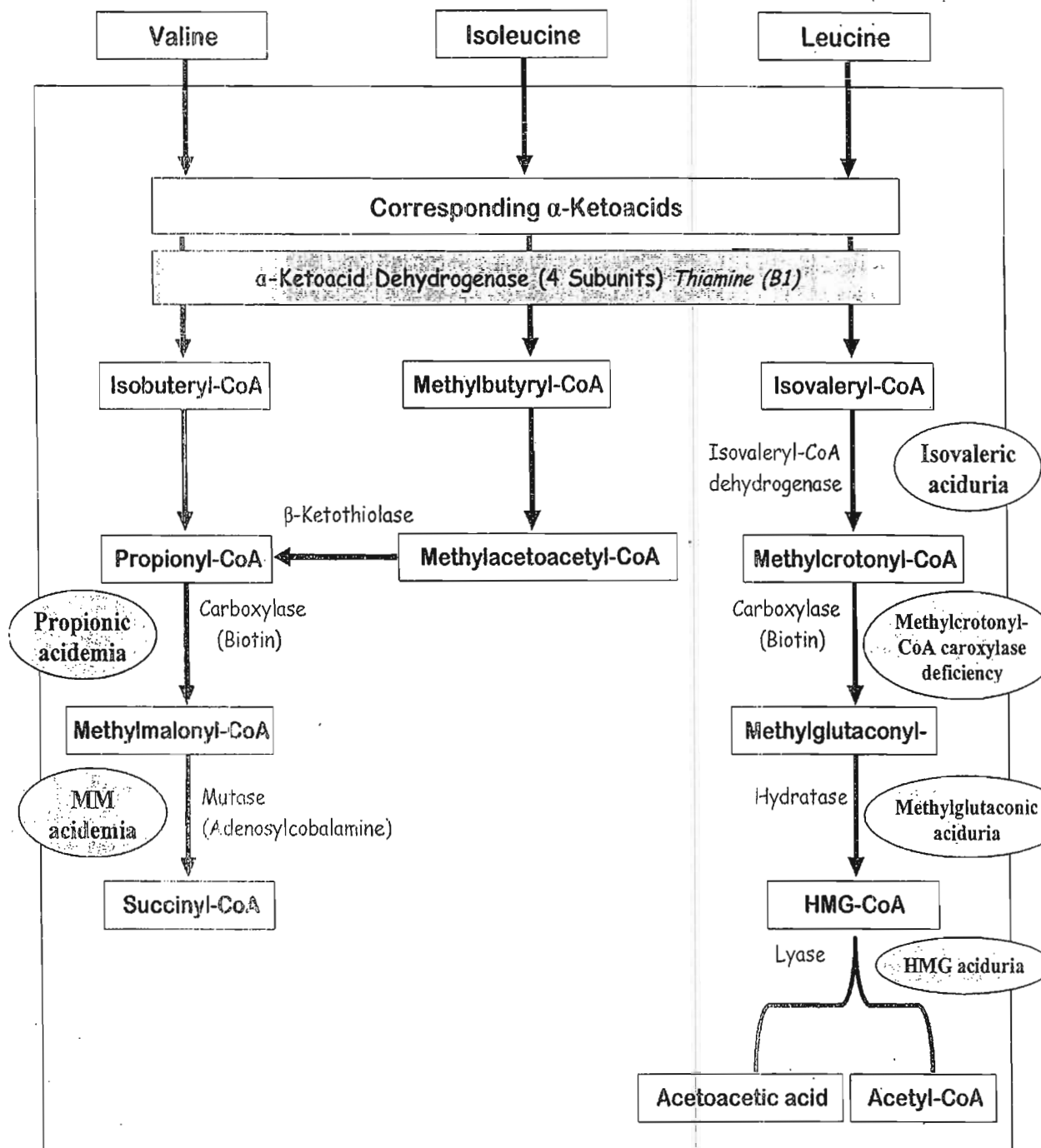
### ▪ Blood ammonia in healthy neonates

- Blood ammonia is higher in neonates than adults
- Level may be up to 100 μmol/L in FT neonates & 150 μmol/L in preterm neonates
- Persists for few weeks
- Asymptomatic

### ▪ Severe Transient Hyperammonemia

- Unknown cause
- Usually preterm with RDS
- Level may be up to 4.000 μmol/L
- Rx of hyperammonemia

# Valine, Leucine & Isoleucine (&Related Organic Acidemias)



# Maple Syrup Urine Disease

### Definition

- AR Deficiency of branched-chain  $\alpha$ -ketoacid dehydrogenase (B<sub>1</sub> is cofactor)
- 1: 185.000

### Biochemical Defect

- VIL (essential branched-chain amino acids)
- $\alpha$ -ketoacid dehydrogenase consists of 4 subunits (E<sub>1 $\alpha$</sub> , E<sub>1 $\beta$</sub> , E<sub>2</sub>, E<sub>3</sub>) coded by different genes
- E<sub>3</sub> is shared with other dehydrogenases (PDH,  $\alpha$ -ketoglutarate dehydrogenase)
- MSUD has 5 phenotypes: Classic, intermittent, mild, thiamine responsive & E<sub>3</sub> deficiency

### Clinical Picture

- At birth: Normal
- First week: Poor feeding, vomiting, lethargy, coma, seizures, hypertonia, opisthotonos
- Peculiar odor: Maple syrup

### Investigations

- Neonatal screening
- Hypoglycemia, metabolic acidosis
- $\uparrow\uparrow$  VIL in plasma & urine
- CT: Brain edema
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

Renal clearance of branched-chain aa is poor, so...

### Treatment

- Acute stage: Hydration, adequate calories, dialysis (PD or HD), mannitol, diuretics?
- After recovery: VIL restricted diet [ $\downarrow\downarrow$  VIL leads to C/P similar to acrodermatitis enteropathica]
- Liver transplantation

### Phenotypes of MSUD

	Classic MSUD	Intermittent MSUD	Mild MSUD	B <sub>1</sub> -responsive MSUD	E <sub>3</sub> subunit deficiency
Enzyme activity		20%	30%	40%	
Clinical Picture		Similar C/P occurs during stress or other catabolic conditions	Milder C/P Trial of B <sub>1</sub> is recommended	Clinical & biochemical improvement with B <sub>1</sub> (10-200 mg/d)	MSUD Lactic acidosis No effective Rx



# **Propionic Acidemia**

## **Definition**

- AR (13q & 3q)
- Deficiency of **propionyl-CoA carboxylase** (Biotin is cofactor)
- 1: 5.000 (in KSA)

## **Biochemical Defect**

- Propionyl-CoA carboxylase consists of 2 subunits ( $\alpha$  &  $\beta$ ) coded by 2 genes
- Cerebral atrophy & destruction of the BG (Metabolic stroke)

## **Clinical Picture**

- At birth: Normal
- First few days: Poor feeding, vomiting, lethargy, coma, seizures, hypotonia, acidosis
- Survivors develop recurrences triggered by infection, constipation or high-protein diet
- Older children: MR, dystonia

## **Investigations**

- Neonatal screening
- Metabolic acidosis (AG), ketosis, hypoglycemia, hyperammonemia (why?)
- **CBC:** Neutropenia, thrombocytopenia, anemia
- $\uparrow\uparrow$  Glycine (*Ketotic hyperglycinemia*)
- $\uparrow\uparrow$  Propionic acid in plasma & urine
- CT: Metabolic stroke
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

## **Treatment**

### **A. Acute attack:**

- Hydration
- Adequate calories with protein restriction
- TTT of hyperammonemia
- GIT sterilization: Oral neomycin or metronidazole
- Carnitine supplementation
- Oral biotin (10 mg/day)
- Dialysis: PD or HD

### **B. Long-term management:**

- Adequate calories
- Protein restriction (Synthetic proteins deficient in propionic acid precursors are available?)
- Carnitine supplementation
- Chronic acidosis: alkali therapy
- Hyperammonemia?

# **Methylmalonic Acidemia**

## **Definition**

- AR
- Deficiency of **methylmalonyl-CoA mutase** or its coenzyme **adenosylcobalamin**
- 1: 48.000 (all forms)

## **Biochemical Defect**

- ↓↓ Methylmalonyl-CoA mutase may be  $mut^0$  (*absent activity*) or  $mut^-$  (*Decreased activity*)
- Seven defects in the intracellular metabolism of vitamin B12 (Cobalamin)
  - *cblA, cblB, cblD*  $\Rightarrow$  Adenosylcobalamin (MMA)
  - *cblC, cblF, cblD*  $\Rightarrow$  Adenosyl- & Methylcobalamin (MA & Homocystinuria)
  - *cblE, cblG, cblD*  $\Rightarrow$  Methylcobalamin (Homocystinuria)
- C/P due to  $mut^0$ ,  $mut^-$ , *cblA, cblB, cblD* are similar
- Cerebral atrophy & destruction of the BG (Metabolic stroke)

## **Clinical Picture**

- ...
- ~~4~~...
- **Complications:** CRF, neurological, acute & recurrent pancreatitis

## **Investigations**

- ↑↑ Methylmalonic acid in plasma & urine

## **Treatment**

### **A. Acute attack:**

- Vitamin B12 (1 mg/day)

### **B. Long-term management:**

- Liver transplantation, renal transplantation

# **Isovaleric Acidemia**

## **Definition**

- AR
- Deficiency of **isovaleryl-CoA dehydrogenase**
- 1: 100.000

## **Clinical Picture**

- Acute form: ...
- Chronic intermittent form: ...

## **Investigations**

- Neonatal screening
- Metabolic acidosis (AG), ketosis, hyperglycemia, hyperammonemia
- **CBC:** Neutropenia, thrombocytopenia, anemia
- ↑↑ Isovaleric acid in plasma & urine
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

## **Treatment**

- Acute
- Long-term management

# **Hyperoxaluria & Oxalosis**

## **Types**

### **☒ Primary hyperoxaluria:**

- Type I: Deficiency of alanine:Glyoxylate aminotransferase
- Type II: Deficiency of D-glycerate dehydrogenase

### **☒ Secondary hyperoxaluria:**

- Pyridoxin deficiency
- High doses of vitamin C
- GIT cause: IBD, bowel resection
- Dietary: Spinach

## **Primary Hyperoxaluria Type I**

### **Biochemical Defect**

- Alanine:Glyoxylate aminotransferase is a peroxisomal enzyme
- The commonest mutation results in **mistargeting** of the enzyme to the mitochondria
- AR (2q)

### **Clinical Picture**

- Renal stones & nephrocalcinosis: Renal colics, hematuria, renal impairment
- Arthritis, crystalline retinopathy

### **Investigations**

- ↑↑ Urinary oxalate (also ↑↑ Glyoxylic & glycolic acid)
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

### **Treatment**

- Pyridoxine especially in patients with...
- Combined liver & kidney transplantation

## **Primary Hyperoxaluria Type II**

### **Biochemical Defect**

- Deficiency of D-glycerate dehydrogenase
- AR (9cen)

### **Clinical Picture**

- Renal failure is less common

### **Investigations**

- ↑↑ Urinary oxalate (Normal urinary glyoxylic & glycolic acid)

### **Treatment**

- No effective TTT

# **Pyridoxine-Dependent Epilepsy**

## **Etiology**

- a. Antiquitin deficiency\*: Enzyme in the catabolic pathway of lysine
- b. Hypophosphatasia: ALP is important for dephosphorylation of P5P

**Clinical Picture** Generalized intractable seizures (1<sup>st</sup> few hours)

**Investigations** EEG

**Treatment** Pyridoxine (5-100 mg/Kg): Dramatic response

Trial of pyridoxine is recommended in any infant with intractable seizures

# **Glutaric Aciduria Type I**

## **Definition**

- AR
- Deficiency of Glutaryl CoA dehydrogenase enzyme (Riboflavin is a cofactor)

## **Clinical Picture**

- Macrocephaly, hypotonia, loss of head control, seizures, dystonia, acidosis

## **Investigations**

- Neonatal screening
- Metabolic acidosis, ketosis, hypoglycemia, hyperammonemia
- ↑↑ Glutaric acid in urine, plasma & CSF
- Enzyme assay & gene analysis
- Prenatal diagnosis is available

## **Treatment**

- Protein restriction
- Riboflavin, L-carnitine, Strychnine & phenytoin: some benefit

# **Canavan Disease**

## **Etiology**

- AR disease (More prevalent in Jews)
- Deficiency of aspartoacylase enzyme (↑↑ N-acetylaspartic acid in CNS, blood & urine)

**Pathology** Spongy degeneration of the white matter

## **Clinical Picture**

- Macrocephaly, severe hypotonia followed by hypertonia & spasticity
- Joint stiffness & contractures
- Seizures, feeding difficulties, aspiration

DD: CP

## **Investigations**

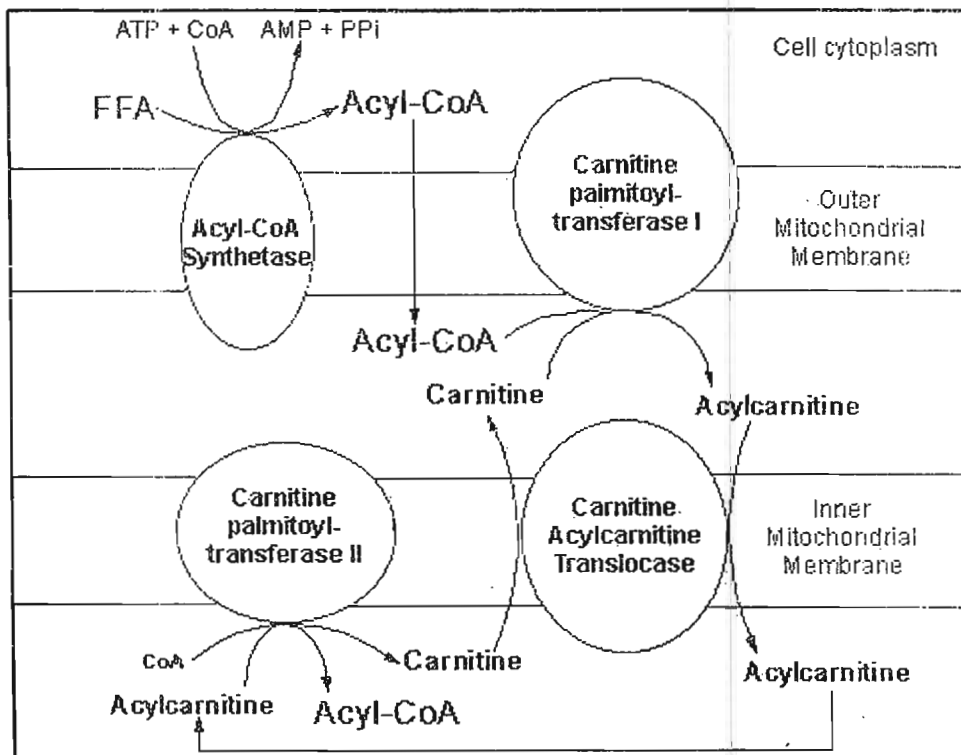
- ↑↑ Urinary & CSF N-acetylaspartic acid
- Enzyme assay: aspartoacylase enzyme
- MRI: White matter degeneration in the cerebral hemispheres
- MRS: High peak of N-acetylaspartic acid

**Treatment** (No specific Rx)

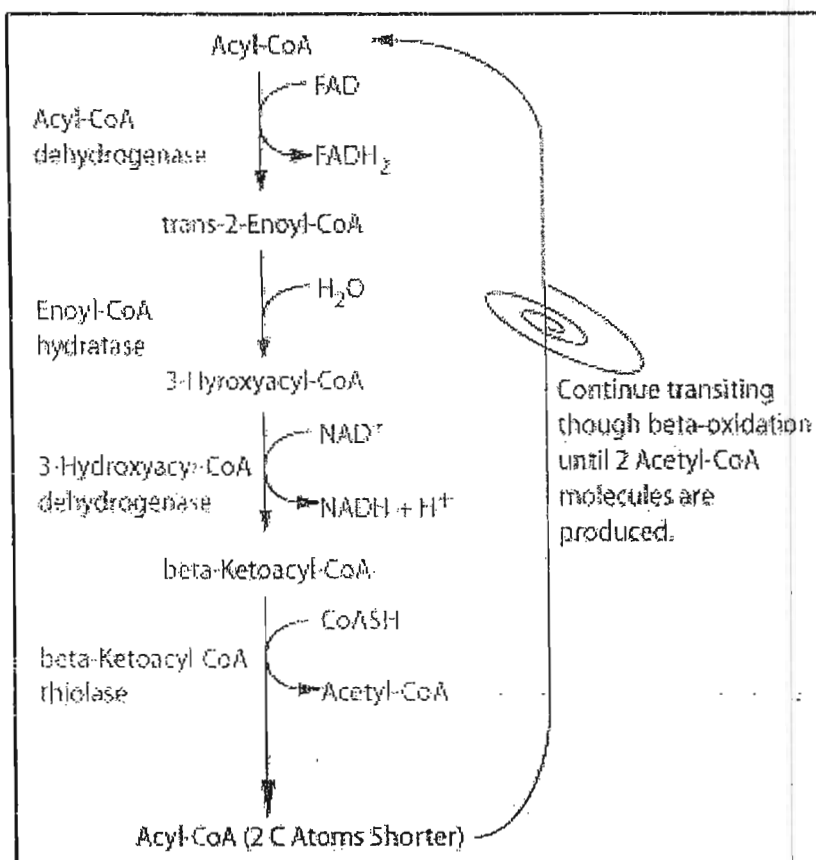
- Trials of aspartoacylase

# Fatty Acid Oxidation

## Carnitine Shuttle



## Steps of $\beta$ -FA oxidation



Acyl-CoA Dehydrogenase

???

Hydratase

Hydroxy  
Acyl-CoA Dehydrogenase

$\beta$ -Ketothiolase

Energy

## **Importance of FA Oxidation**

- Starvation, Relation to Ketogenesis
- ↓↓ Caloric intake (.....)
- Exercise
- Heart?
- Brain?

## **Types of FA Oxidation**

- ☒  $\beta$ -FA oxidation
- ☒  $\alpha$ -FA oxidation
- ☒ Peroxisomal FA oxidation

## **General C/P of FA Oxidation**

- Inheritance: All are AR
  - Incidence: FA oxidation disorders combined are common
  - May be asymptomatic?
  - Organs affected?
    - Liver: Hypoketotic hypoglycemia, coma (ALTE)
    - Skeletal muscles: Exercise intolerance & exercise-induced rhabdomyolysis
    - Heart: Cardiomyopathy
    - Kidneys: RTA
  - Other manifestations
    - Fatty liver of pregnancy or preeclampsia with HELLP:
      - When? Fetus                      Mother
      - HELLP: Hémolysis, Elevated liver enzymes, Low platelet count
      - Mechanism: Related to toxic effect of FA rather than...
      - Types: LCHAD, TFP, CPT-1 deficiency
    - Congenital malformations (Brain & Kidneys):
      - Mechanism: Related to toxic effect of FA rather than...
      - Types: ETF, ETF-DH, CPT-II
    - Pigmented retinopathy
    - Progressive liver disease
    - Peripheral neuropathy
- } *LCHAD/TFP deficiency*
- The only specific clue for diagnosis is **hypoketotic hypoglycemia**
  - Neonatal screening: characteristic acylcarnitines
  - DD: Reye syndrome, SIDS

# Peroxisomal Disorders

## Classification

### A. Peroxisomal biogenesis defects:

- Failure to import one or more proteins into the peroxisomes
- Peroxisomes: Absent or decreased
- Abnormalities of multiple peroxisomal functions are present
- Disorders:

- ☒ Zellweger syndrome (ZS)
- ☒ Neonatal adrenoleukodystrophy (NALD)
- ☒ Infantile Refsum disease (IRD)
- ☒ Rhizomelic chondrodysplasia punctata (RCDP)

*Zellweger spectrum disorders*

### B. Single enzyme defect

- Defect in the function of a single peroxisomal enzyme
- Peroxisomes: Normal number & structure
- Abnormality of single peroxisomal function
- Disorders:

- ☒ X-linked adrenoleukodystrophy
- ☒ Acyl CoA oxidase deficiency
- ☒ Peroxisomal thiolase deficiency
- ☒ Classic Refsum disease

- ☒ Mevalonic aciduria
- ☒ Glutaric aciduria type III
- ☒ Hyperoxaluria type I
- ☒ Acatalasemia

## Epidemiology

- 1:50.000 live births
- X-ALD is the commonest (1:20.000)
- All are AR except...
- Antenatal diagnosis is available

## Pathology

- PBD: Absent or decreased peroxisomes with peroxisome "Ghosts"
- Multisystem affection:
  - a. **Nervous system:** Defect in neuronal migration, MR, hypotonia
  - b. **Liver:** Hepatomegaly, cirrhosis
  - c. **Skeletal:** Chondrodysplasia punctata
  - d. **Eye:** Cataract, glaucoma, retinopathy
  - e. **Heart:** CHD
  - f. **Dysmorphic features**

**Mechanism?**

## Refsum Neuropathy

**Etiology** AR<sup>10</sup> (Phytanoyl CoA oxidase)

**Pathogenesis** Failure of  $\alpha$ -FA oxidation → accumulation of phytanic acid

**C/P** Polyneuropathy, ataxia, retinitis pigmentosa, blindness, deafness, ichthyosis (scaly skin)

**Investigations** ↑↑ Serum phytanic acid, ↓↓ NCV

**Treatment** ↓↓ Dietary phytanic acid (nuts, coffee)  
Plasmapheresis

# **Zellweger Syndrome**

## **Genetics**

- AR; most common cause are mutation in **PEX1** & **PEX6**

**DD?**

## **Clinical Picture**

- Dysmorphic facies: high forehead, hypoplastic supraorbital ridges, epicanthal folds, midfacial hypoplasia, large fontanel
- Ocular: Cataract, glaucoma, corneal clouding, brush-field spots, nystagmus, optic nerve hypoplasia, pigmentary retinopathy
- Hypotonia, seizures, psychomotor retardation, sensorineural deafness
- Hepatomegaly, cholestasis, cirrhosis
- Renal cysts

# **Neonatal Adrenoleukodystrophy**

## **Genetics**

- AR, mutation in PEX genes (e.g., PEX1...)

## **Clinical Picture**

- Dysmorphic facies: Few or absent
- Ocular: Pigmentary retinopathy
- Hypotonia, seizures, psychomotor retardation, sensorineural deafness
- Hepatomegaly, cholestasis, cirrhosis
- Adrenal function is usually impaired

# **Infantile Refsum Disease**

## **Genetics**

- AR, mutation in PEX genes (e.g., PEX1...)

## **Clinical Picture**

- Dysmorphic facies: Few or absent
- Ataxia (broad based gait)
- Ocular: Pigmentary retinopathy
- Hypotonia, seizures, **psychomotor retardation**, sensorineural deafness
- Hepatomegaly, cholestasis, cirrhosis

# **Rhizomelic chondrodysplasia**

## **Punctata**

## **Genetics**

- AR, mutation of PEX7 (receptor for PTS2)

## **Clinical Picture**

- Disproportionate short stature (Rhizomelic = )
- Dysmorphic facies: Depressed nasal bridge, hypertelorism
- Cataract, psychomotor retardation, ichthyosis, quadriplegia (why?)

## **Investigations**

- Radiology: epiphyseal stippling, vertebral body clefts





## **Approach to Diagnosis of Peroxisomal Disorders**

### **A. Level 1: Confirm the diagnosis of peroxisomal disorder**

- VLCFA: ↑↑ (Normal in RCDP)
- Phytanic acid
- Pipecolic acid
- RBC plasmalogen
- Bile acids

### **B. Level 2: Precise nature of the peroxisomal disorder**

Disorder	VLCFA	RBC plasmalogen	Pipecolic acid	Phytanic acid	Bile acid
ZS, NALD, IRD	↑↑	↓↓	↑↑	↑↑	↑↑
RCDP	N	↓↓	N	↑↑	N
Classic Refsum	N	N	N	↑↑	N
X-ALD	↑↑	N	N	N	N
Bifunctional enzyme	↑↑	N	N	↑↑	↑↑

### **C. Level 3: Molecular defect of peroxisomal disorder: PEX genes**

#### **Treatment**

- Classic Refsum disease:
- Supportive TTT
- Oral docosahexaenoic acid

# Adrenoleukodystrophy

## Definition

- Peroxisomal disorder characterized by accumulation of VLCFA in CNS & adrenal cortex
- Neonatal ALD & XL-ALD

## XL-Adrenoleukodystrophy

### Etiology

- Defect in peroxisomal degradation of VLCFA (Due to  $\downarrow\downarrow$  lignoceroyl CoA ligase)
- Accumulation of VLCFA in CNS & adrenal cortex
- Not rare; 1:20.000 ♂

### Pathogenesis

- Accumulation of VLCFA  $\rightarrow$  adrenal dysfunction
- CNS: Inflammation (Demyelination); mostly in the parieto-occipital area

### Clinical Picture "Five phenotypes are recognized"

#### A) Childhood cerebral form

- Onset: 4-8 years
- Hyperactivity (DD: ADHD), academic deterioration
- Impaired auditory discrimination, visual disturbance, ataxia
- Seizures, spastic quadriplegia
- Bulbar manifestations
- $\uparrow\uparrow$  ICT, unilateral mass lesion
- **Adrenal insufficiency:** Usually follows but may precede neurologic manifestations

#### B) Adolescent ALD: Delayed onset & less progressive course

#### C) Adrenomyeloneuropathy

- Affection of spinal cord & peripheral nerves in adolescents & adults
- Progressive paraparesis, urinary incontinence, impotence

#### D) Addison only: 25% of Addison patients have biochemical defects of ALD, so...

#### E) Asymptomatic ALD

**NB:** 50% of heterozygous ♀ may have milder adrenomyeloneuropathy

### Investigations

- $\uparrow\uparrow$  VLCFA in plasma, RBC, fibroblasts
- CT, MRI: Typically symmetric periventricular in the posterior parietal & occipital lobes  
Unilateral lesion with mass effect (DD: Tumor) may occur
- Adrenal function tests: ACTH, cortisol after ACTH stimulation

### Treatment

- **BMT:** Considered in neurologically asymptomatic or mildly affected patients
- **Lorenzo's oil:**  $\downarrow\downarrow$  VLCFA synthesis
- **Adrenal replacement**

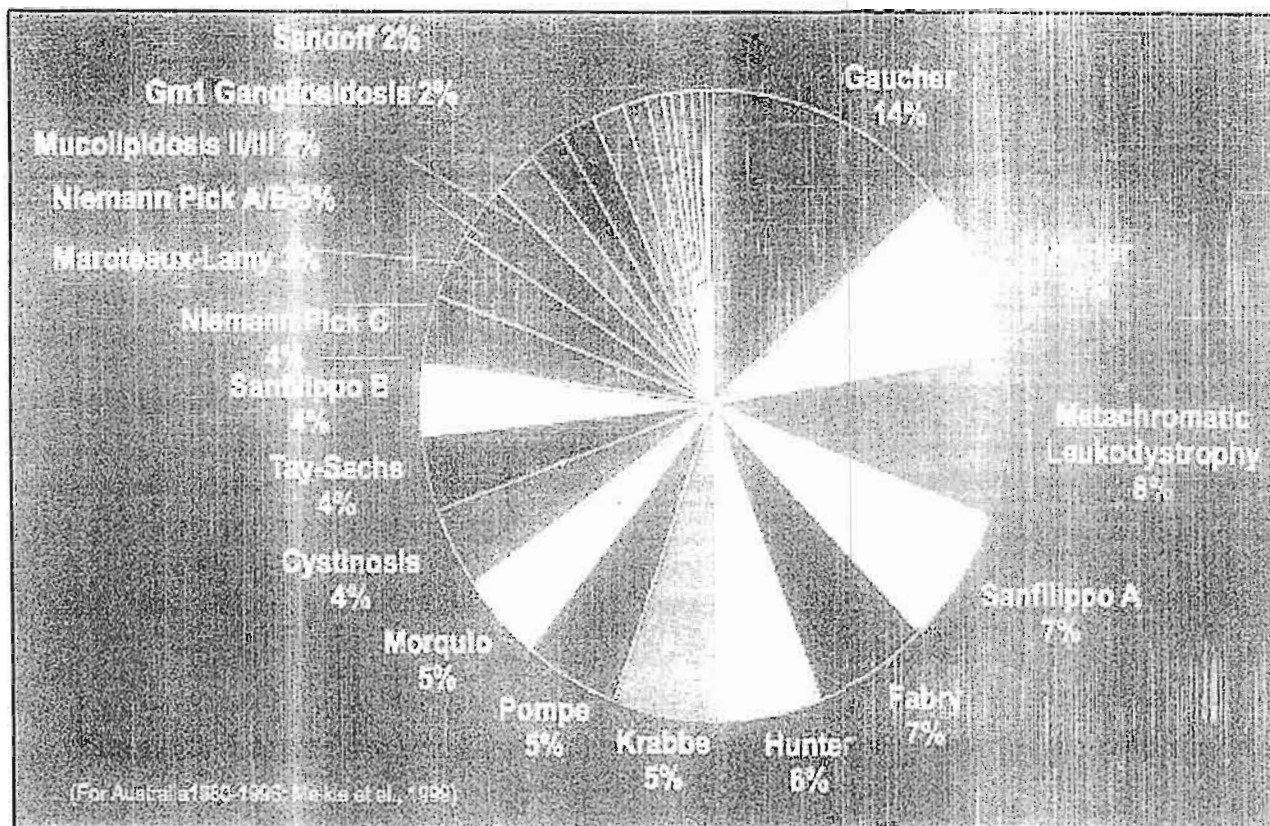
### Prevention & Genetic counseling

- **Family screening:** VLCFA (allows early diagnosis of presymptomatic individuals, why?)
- **Antenatal diagnosis:** VLCFA (amniocytes or CVS) or molecular testing
- **Addison males**

**DD** ADHD, other leukodystrophies, MS, brain tumors, epilepsy, Addison



## **Lysosomal Disorders**



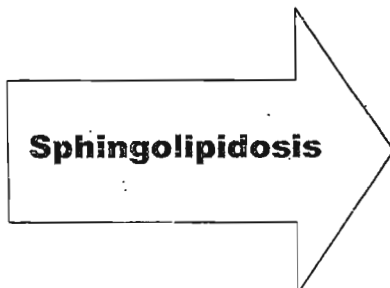
### **Lysosomal Storage Diseases:**

1. Sphingolipidosis (6 + 4)
2. MPS
3. Mucopolipidosis
4. Fucosidosis
5. NCL
6. Sialidosis

# Sphingolipidosis

## Definition

- Group of diseases characterized by accumulation of sphingolipids
- Sphingolipids: Sphingosine-containing lipids (*Cerebrosides, gangliosides*)
- Sphingosine is an amino alcohol



### **Sphingolipidosis:**

1. GM 1 Gangliosidosis
2. GM 2 Gangliosidosis
3. Krabbe disease (KD)
4. Metachromatic LD
5. Gaucher
6. Niemann-Pick

### **Other**

### **Sphingolipidosis:**

1. Fabry
2. Farber
3. Wolman
4. Multiple sulfatase deficiency

## Gaucher Disease

### Etiology

- Glucocerebrosidase ( $\beta$ -Glucosidase) deficiency (AR<sup>1</sup>)
- **Four** mutations account for the majority of cases
- Incidence in Jews = 1/1.000
- Carrier rate in Jews = 1/18

**Gaucher should be considered in the DD of any child with unexplained organomegaly**

### Clinical Picture

	<b>Type 1* (99%)</b>	<b>Type 2</b>	<b>Type 3</b>
<b>Other Names</b>	Adult type Non-Neuropathic	Infantile Acute neuropathic	Juvenile Subacute neuropathic
<b>Onset</b>	Variable	Infancy	Early childhood > 2yrs
<b>C/P</b>	<ul style="list-style-type: none"> <li>▪ HSM (S &gt; L)</li> <li>▪ Anemia</li> <li>▪ Thrombocytopenia</li> <li>▪ Bruises</li> <li>▪ Bony pains</li> <li>▪ Pathologic fractures</li> <li>▪ Normal mentality</li> <li>(?? Chronic disease)</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ Hypertonia</li> <li>▪ Head retraction</li> <li>▪ Laryngospasm</li> <li>▪ Stridor</li> <li>▪ Squint</li> <li>▪ Cranial nerve...</li> <li>▪ Rapid <b>neurologic</b>...MR</li> <li>▪ Death in the 1<sup>st</sup> 2 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ <b>Neurologic</b> (Less severe)</li> <li>▪ MR</li> <li>▪ Ataxia</li> <li>▪ Myoclonic epilepsy</li> <li>▪ Gaze palsy</li> <li>▪ Death by age of 10-15 y</li> </ul>

### Investigations

- X-rays: Lytic lesions, Erlenmeyer flask deformity (Distal femur)
- BM examination: Gaucher cells (Positive PAS stain)
- Enzyme assay: Leukocytes or fibroblast
- Carrier detection: Molecular testing (4)
- Antenatal diagnosis is available

**Not Pathognom**

### Treatment

- Enzyme replacement: Cerezyme (IV infusion every other week): No effect on CNS
- BMT
- Gene therapy

## Niemann-Pick Disease

### Etiology

- Type A & B: Sphingomyelinase deficiency (AR<sup>11</sup>)
- Type C: Defective cholesterol transport (with 2ry sphingomyelinase deficiency)

### Clinical Picture

	Type A	Type B	Type C
Other Names	Acute infantile	Non-Neuropathic	Neuropathic
Onset	1 <sup>st</sup> few months of life	Infancy or childhood	Early childhood > 2yrs
C/P	<ul style="list-style-type: none"> <li>▪ HSM (L &gt; S)</li> <li>▪ FTT, feeding difficulties</li> <li>▪ Neurological...MR</li> <li>▪ Cherry-red spots (50%)</li> <li>▪ Spasticity</li> <li>▪ Death in the 1<sup>st</sup> 3 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ HSM</li> <li>▪ Pulmonary involvement</li> <li>▪ Dyspnea, pneumonia</li> <li>▪ No neurological...</li> <li>▪ Normal mentality</li> <li>▪ Hypersplenism</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Slowly progressive neurologic course</li> <li>▪ Gaze palsy.</li> <li>▪ HSM (<i>Less severe</i>)</li> </ul>

### Investigations

- BM examination: Foam cells (NP cells)
- Enzyme assay (Leukocytes or fibroblasts)
- CXR (Type B): Reticular or nodular infiltration
- Antenatal diagnosis is available

### Treatment

- Supportive
- Liver transplantation
- Enzyme therapy in type B (Phase I trial)

## Farber Disease

### Etiology

- Ceramidase deficiency (AR)
- Accumulation of ceramide in various tissues, especially the joints

### Clinical Picture

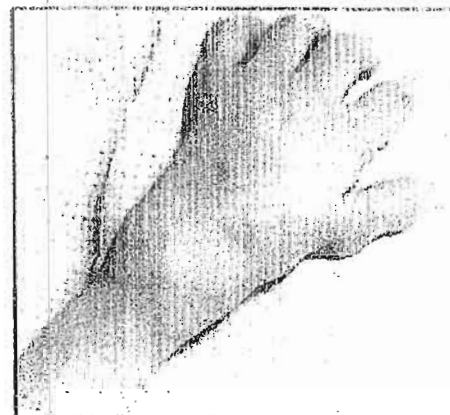
- Onset: 1<sup>st</sup> year of life
- Joint: Painful swelling & nodules
- Vocal cord nodules: Hoarseness of voice

### Investigations

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

### Treatment

- Supportive



## Fabry Disease

(See before)

# **Gangliosidosis**

**Definition** Accumulation of gangliosides (Glycosphingolipids)

## **GM1 Gangliosidosis**

### **Etiology**

-  $\beta$ -Galactosidase deficiency (AR<sup>3</sup>) → Accumulation of GM1 gangliosides (CNS & viscera)

### **Clinical Picture**

	Infantile*	Juvenile	Adult
Other Names	Type 1	Type 2	Type 3
Onset	Birth	1 year	Adult
C/P	<ul style="list-style-type: none"> <li>▪ Poor feeding</li> <li>▪ HSM</li> <li>▪ Global developmental delay</li> <li>▪ Seizures</li> <li>▪ Spasticity</li> <li>▪ Hurler-like... (Coarse facial feature)</li> <li>▪ Dysostosis multiplex</li> <li>▪ Blindness &amp; Deafness</li> <li>▪ Cherry-red spots</li> <li>▪ Angiokeratoma</li> <li>▪ Death in the 1<sup>st</sup> 3 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Mental retardation</li> <li>▪ Seizures</li> <li>▪ Spasticity</li> <li>▪ Blindness</li> <li>▪ No HSM</li> <li>▪ No Hurler-like...</li> <li>▪ Death in the 1<sup>st</sup> 10 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Spasticity</li> <li>▪ Dysarthria</li> <li>▪ ↓↓ Cognitive function</li> </ul>

## **GM2 Gangliosidosis**

### **Etiology**

- Tay-Sachs: AR<sup>15</sup> Sandhoff: AR<sup>5</sup>
- Carrier rate of Tay-Sachs in Jews = 1/25

### **Clinical Picture**

	Tay-Sachs	Sandhoff	Juvenile & Adult
Genetics	HEXA gene (Chromosome 15)	HEXB gene (Chromosome 5)	-
Defect	Hexosaminidase A	Hexosaminidase A & B	
Onset	5-6 months		Childhood-adult
C/P	<ul style="list-style-type: none"> <li>▪ Marked startle reaction (= Hyperacusis)</li> <li>▪ Regression</li> <li>▪ No HSM</li> <li>▪ Seizures</li> <li>▪ Splenomegaly (HSM) in Sandhoff</li> </ul>	<ul style="list-style-type: none"> <li>▪ Early hypotonia → Spasticity</li> <li>▪ Blindness &amp; Deafness</li> <li>▪ Macrocephaly</li> <li>▪ Cherry-red spots</li> <li>▪ Death in the 1<sup>st</sup> 3-5 yrs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Ataxia</li> <li>▪ Spasticity</li> <li>▪ Dysarthria</li> </ul>

### **Investigations**

- Enzyme assay: Leukocytes or fibroblast
- Antenatal diagnosis & carrier detection is available (Enzyme activity)

**Treatment** Supportive

# **Krabbe Disease**

(Globoid Cell Leukodystrophy)

## **Etiology**

- Galactocerebroside  $\beta$ -Galactosidase deficiency (AR)
- Accumulation of Galactocerebroside  $\rightarrow$  Myelin destruction (Vicious circle)

## **Clinical Picture**

- Onset: 1<sup>st</sup> months of life
- Irritability, crying, spasticity, opisthotonos, Seizures
- Neuropathy, absent deep reflexes

(DD: Colic, milk allergy...)

## **Investigations**

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## **Treatment**

- Stem cell transplantation may improve the outcome if given very early

# **Metachromatic Leukodystrophy**

## **Etiology**

- Arylsulfatase deficiency (AR<sup>22</sup>)
- Accumulation of cerebroside sulfate  $\rightarrow$  Myelin destruction (*CNS & peripheral nerves*)
- Classified into: Late infantile, juvenile & adult types

## **Clinical Picture**

- Onset: 1-2 year
- Regression (Loss of ability to walk...)
- Hypotonia, Seizures
- Neuropathy, absent deep reflexes

## **Investigations**

- $\downarrow\downarrow$  NCV,  $\uparrow\uparrow$  CSF proteins
- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

## **Treatment**

- Stem cell transplantation may improve the outcome if given very early

# **Wolman Disease**

**Etiology** Acid lipase deficiency (AR)  $\rightarrow$  Accumulation of cholesterol esters

**Clinical Picture** FTT + Steatorrhea + HSM + Calcification of the adrenal glands

# **Neuronal Ceroid Lipofuscinosis**

## **Definition**

- Lysosomal storage disorder
- Intracellular accumulation of fluorescent lipopigments, ceroid & lipofuscin
- NCL is characterized by visual loss, seizures, motor deterioration & early death
- Traditionally classified into: Infantile, Late infantile & juvenile types

# Mucopolysaccharidosis

## Biochemistry

- ☒ **Monosaccharide:** Glucose, Galactose, Fructose
- ☒ **Disaccharide:** Maltose, Lactose, Sucrose
- ☒ **Polysaccharide:**
  - Homo-: Glycogen, Starch, Inulin, Agar
  - Hetero-: Glycosaminoglycans (= MPS)

### GAG:

- Chondroitin sulfate
  - Dermatan sulfate
  - Keratan sulfate
  - Heparan sulfate (CNS)
  - Hyaluronic acid
- } (CT)

## Definition

- Lysosomal inherited disorders caused by incomplete degradation & storage of GAG
- MPS-III is the most common followed by MPS-I & II
- Incidence = 4: 100.000

## Mode of Inheritance

All are AR except Hunter (Type II)

## Clinical Picture

- Normal at birth, Why???
- Progressive course
- Nasal discharge
- All have corneal Clouding except... *hunter*
- Deafness in Type...
- Hernia (Recurrent)
- Main organs: Bones, Cartilages, Joints, Tendons, CT, Skin, CNS

## Classification

With...	Without...
Hurler syndrome (Type I-H)	Morquio syndrome (Type IV)
Hunter syndrome (Type II)	Scheie syndrome (Type V = Type I-S)
Sanfilippo syndrome (Type III)	Maroteaux-Lamy syndrome (Type VI)

- **Sly disease (Type VII):** Wide range of clinical involvement (Fetal hydrops- delayed onset)
- **Type IX:** Periarticular soft tissue masses & short stature

## Dysostosis Multiplex

- Radiological changes
- Features
  - Skull: Macrocephaly, Dolicocephaly, J-shaped sella turcica
  - Clavicles: Thickening of the medial 1/3
  - Ribs: Spatulated (oar-shaped)
  - Vertebrae: Ovoid with anterior beaking
  - Iliac bones: Flaring
  - Radius & Ulna: Abnormal with V-shaped articulation
  - Metacarpals: Pointed proximally (5<sup>th</sup>\*)
  - Phalanges: Pointed distally (bullet-shaped)

## Diagnosis

- ☒ **Clinical**
- ☒ **Radiological:** Dysostosis multiplex
- ☒ **Urinary GAG**
- ☒ **Enzyme assay** (Serum, WBC, Fibroblasts):  $\alpha$ -L-Iduronidase in MPS-I-H



## **MPS-I**

### **Hurler Syndrome**

1. **At birth:** Normal (Diagnosis is usually made between 6-24 months)
2. **1<sup>st</sup> year:**
  - Persistent nasal discharge & obstruction
  - MR, HSM, Kyphosis
3. **After the 1<sup>st</sup> year**
  - Nasal discharge, MR, HSM, Kyphosis
  - Obstructive airway disease (OSA)
  - Coarse facies: Coarse hair, large head, hypertelorism, depressed nasal bridge, low-set ears, macroglossia, thick lips
  - Cardiac: Cardiomyopathy, coronary stenosis, valvular affection (AR, MR)
  - Hydrocephalus (Communicating)
  - Skeletal: Joint stiffness, claw hand, kyphosis, hernia, X-rays (Dysostosis multiplex)

**$\alpha$ -L-Iduronidase**

**Most severe**

### **Scheie Syndrome**

1. Previously called Type V
2. C/P appears after the age of 5 years
3. Corneal clouding
4. Claw hand
5. Carpal tunnel syndrome
6. Aortic regurgitation
7. Normal mentality

**Mildest**



### **MPS-II Hunter Syndrome**

1. As Hurler but milder
2. XLR, No Corneal clouding
3. Deafness
4. Hydrocephalus
5. Skin papules

**Iduronate-2- sulfatase**

**XLR    الوحيد**  
**No corneal clouding    الوحيد**

### **Sanfilippo Syndrome**

1. Rapid neurological deterioration
2. Severe MR
3. Mild dysmorphism

**Neurological**

### **Morquio Syndrome**

1. Short stature
2. Skeletal: Kyphosis, flat feet, genu valgum, platyspondyly
3. HSM, corneal clouding...
4. Small separated teeth, broad mouth
5. Atlant-oaxial instability

**Skeletal**

**$\beta$ -Galactosidase**

**No MR**

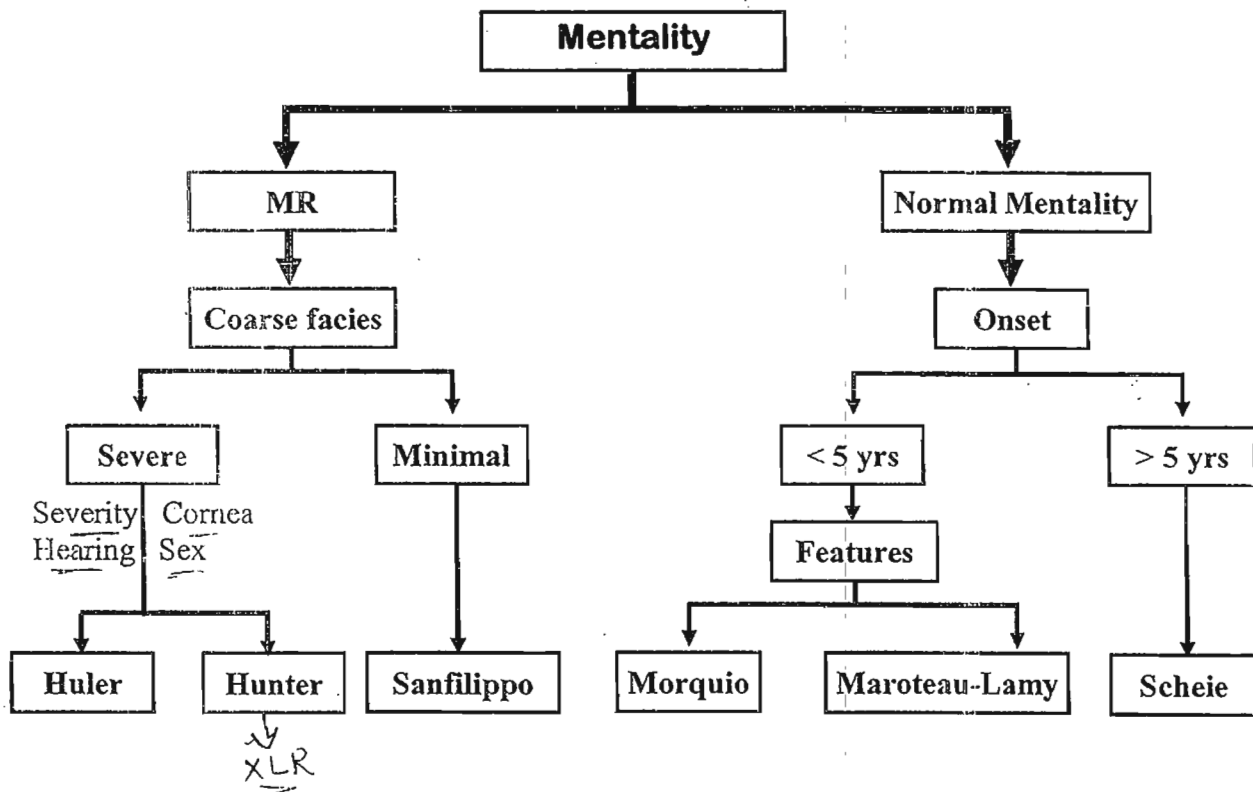
### **Maroteaux-Lamy Syndrome**

1. As Hurler but delayed onset & slower course
2. Normal mentality

**Arylsulfatase B**

**No MR**

## Clinical Approach to a case of MPS



### Regular Assessment

- ☒ General history & examination
- ☒ Audiometry
- ☒ Visual acuity, corneal & retinal examination
- ☒ FVC & sleep study
- ☒ ECG, Echo

### Treatment

- ☒ HSCT: MPS I, II, VI
- ☒ Enzyme replacement: HSCT: MPS I, II, VI
- ☒ Combined
- ☒ Multidisciplinary care

### Hurler-like Diseases:

1. GM 1 Gangliosidosis
2. Mucopolipidosis
3. Fucosidosis
4. Sialidosis type II
5. Mannosidosis

# Glycogen Storage Diseases

## Types

Disease	Enzyme Defect	Clinical Picture
<b>Type Ia</b> (Von Gierke)	G-6-Phosphatase	Doll face Marked Hepatomegaly Fasting hypoglycemia (Seizures) Hypercholesterolemia Lactic acidosis ↑↑ Uric acid
<b>Type Ib</b>	G-6-Phosphate Translocase	GSD I + Neutropenia
<b>Type II</b> (Pompe)	Acid maltase	Hepatomegaly Myopathy Cardiomyopathy
<b>Type III</b> (Cori)	Debranching	Hepatomegaly Hypoglycemia Myopathy
<b>Type IV</b> (Andersen)	Brancher	HSM Liver cirrhosis LCF Ascites
<b>Type V</b> (Mc Ardle)	Muscle Phosphorylase	Exercise intolerance Muscle cramps Easy fatigability
<b>Type VI</b> (Hers)	Liver Phosphorylase	
<b>Type VII</b> (Tauri)	PFK	V + Hemolytic anemia
<b>Type VIII</b>		?? Ataxia
<b>Type IX</b>	Phosphoglycerate Kinase	
<b>Type X</b>		
<b>Type XI</b> (Fanconi-Bickel)	Glucose Transporter II	FTT + Fanconi + Hepatomegaly
<b>Type 0</b>	Glycogen synthase	Fasting hypoglycemia (Seizures) Prolonged hyperglycemia (after meals)

## Diagnosis

- Biochemical
- Liver biopsy
- Enzyme assay (Liver)

## Treatment

- Avoid... *fasting*
- Enzyme?
- Liver transplantation

Hepatic	Muscle	Mixed

# **Galactosemia**

## **Etiology**

1. Galactose 1-P-uridyltransferase deficiency\*\* (Classic Galactosemia)
2. Galactokinase deficiency (Only cataract)
3. Epimerase deficiency

## **Clinical Picture**

- Jaundice (Cholestasis)
- Hepatomegaly, splenomegaly, ascites
- Hypoglycemia, convulsions, lethargy
- FTT, vomiting
- Cataract
- E.coli sepsis

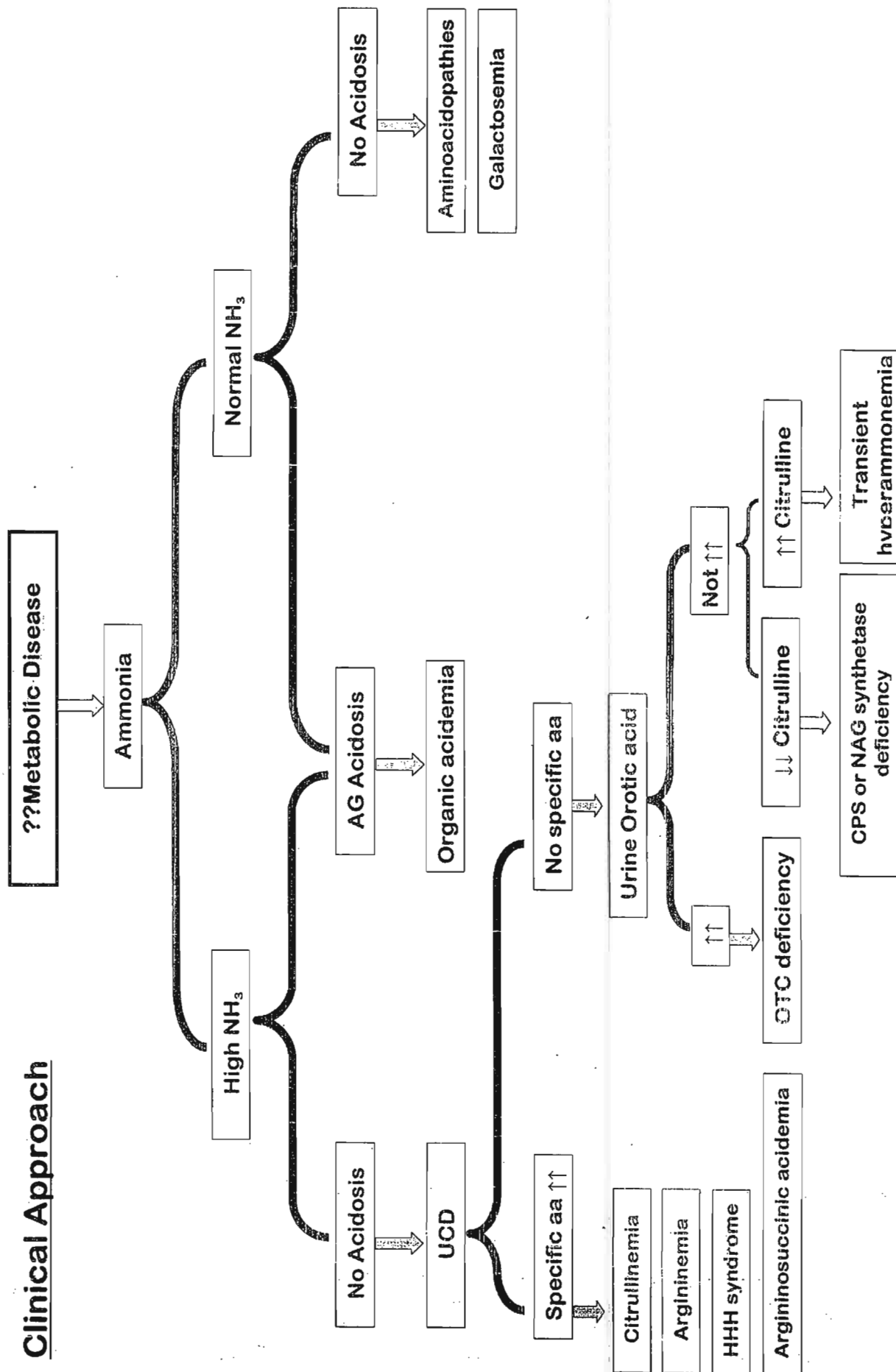
## **Diagnosis**

- Reducing substances in urine (When?)
- Enzyme assay

## **Treatment**

# **Hereditary fructose intolerance**

# Clinical Approach



# Urea Cycle

